A STUDY OF THE METABOLIC ASPECTS OF THERAPY OF RADIATION INJURY IN THE SOLDIER

SEPTEMBER 1969

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THERAPY OF RADIATION INJURY – METABOLIC ASPECTS

SEPTEMBER 1969

FOREWORD

This technical report is the third of three reviews of promising research opportunities to improve the treatment of radiation injury in the soldier. A Study of the Metabolic Aspects of Therapy of Radiation Injury in the Soldier complements the first report on A Study of the Immunologic Aspects of Therapy of Radiation Injury in the Soldier (1), and the second report, A Study of Early Radiation-Induced Biological Changes as Indicators of Radiation Injury (2).

Part I of this report was prepared by the Staff of the Life Sciences Research Office, Office of Biomedical Studies, Federation of American Societies for Experimental Biology (FASEB). The text reflects the opinions of an ad hoc study group that met at Beaumont, FASEB, on September 24 and 25, 1968. The report has been approved by the majority, not necessarily by all, of the participants.

Part II of this report is a critical literature review with an annotated evaluative bibliography.

This study was made for the United States Army Medical Research and Development Command, Office of The Surgeon General, Department of the Army, in accordance with the provisions of Contract No. DADA-17-67-C-7180.

SUMMARY

This study is the third in a series to review research on the biological effects of radiation and to explore the possibility of developing better methods to treat radiation-induced injury in the soldier.

Early symptoms produced by whole-body radiation exposure are generally related to the abnormal physiology and cellular lesions of the gastrointestinal tract. These symptoms have diagnostic value but the pathologic changes are not readily amenable to medical treatment. This report reviews recent research on the effects of radiation on the gastrointestinal tract of man and experimental animals including: gastrointestinal symptomatology; immediate post-irradiation cellular events; morphologic responses; gastrointestinal and hematopoietic correlations; intestinal motility and malabsorption; intestinal flora changes; antibiotics in radiation therapy; radiation-induced vomiting; transport of fluid, electrolytes, nutrients, and other essential elements; and alterations in drug metabolism. In reviewing these aspects of the radiation-induced "gastrointestinal syndrome" therapeutic opportunities were identified. Suggested areas for future research emphasis are summarized.

A critical literature review entitled The Gastrointestinal Syndrome in Acute Radiation Injury and an annotated evaluative bibliography constitute Part II of the report.

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I. THE PROBLEM

The United States Army Medical Department has the responsibility for treatment of ionizing radiation injury (radiation injury) in the soldier. To assist in fulfilling this obligation the U.S. Army Medical Research and Development Command, Office of The Surgeon General, Department of the Army, conducts a research program in military nuclear medicine. Study of the metabolic aspects of therapy of radiation injury was selected to complement prior reviews as a portion of a comprehensive analysis of the treatment of radiation injury in the soldier. Many early symptoms of radiation exposure are related to the abnormal gastrointestinal physiology and the pathologic lesions produced by ionizing radiation. These changes have diagnostic value and suggest subsequent medical treatment regimens. In addition, radiation injury may be manifest by modification of the absorption, distribution, utilization, and excretion of essential nutrients, water, and drugs. Most of these changes are observed following exposure to radiation doses great enough to produce the "gastrointestinal syndrome." There is a relative paucity of data correlating the fate of drugs with the post-irradiation state.

The primary interest of the present review is the radiation-induced gastrointestinal injury most likely responsive to treatment following exposure to radiation doses of less than 1000 rad. In this range of radiation the exposed individual may have a good chance of survival. Lower doses in the range 0 to 100 rad will inflict minimal injury. Higher doses will produce injury to the bone marrow, the gastrointestinal tract, and the central nervous system that will probably be lethal. Therefore, the metabolic aspects of therapy, specifically for surviving radiation exposed casualties, have been emphasized in this study.

II. BACKGROUND AND PRELIMINARY CONSIDERATIONS

The symptomatology characteristic of the gastrointestinal syndrome following lethal whole-body exposure originates in the malfunction of the intestinal mucosa and the hematopoietic cell renewal system of the bone marrow. The causes of the ensuing death are the result of complex synergistic phenomena and cannot be ascribed to either system alone. The clinical manifestations of the gastrointestinal syndrome are anorexia, vomiting, diarrhea, fever, and dehydration. Other effects include a loss of weight and impaired absorption from the intestinal tract (3).

Alterations in the physiology of the gastrointestinal tract after lethal radiation exposure include impaired secretion and depression or cessation of intestinal epithelial cell production. The interval preceding death is characterized by uncontrollable diarrhea, protracted and continued vomiting, and exhaustion. The time span from irradiation to death is usually 3 to 4 days.

To study the effects of radiation on a complex physiological process such as gastrointestinal function, requires a sound understanding of the details of the movement of fluid, electrolytes, nutrients, and drugs from the bowel lumen to the blood or lymph.

The possibility of the soldier receiving mechanical and thermal injuries in addition to radiation exposure in the event of a nuclear incident is indeed high. Therefore, various agents, for example anesthetics and antibiotics administered for diagnosis and treatment, may react in an unknown manner that could be detrimental to the irradiated man. It is desirable to understand the various metabolic factors modified by radiation exposure that will influence the required forms of therapy. Altered mechanisms of action or routes of biotransformation may occur if the irradiated individual experiences decreased liver or kidney function or similar changes in other excretory or detoxifying mechanisms.

While many morphological and functional aspects of radiation-induced injury of the gastrointestinal tract have been widely studied, the relative importance of the component derangements in causing morbidity and mortality require further clarification.

Some of the more recent experimental studies, for example, suggest that the repair potential is greater than originally expected. The facts available at this time suggest that future exploration of these developments will significantly improve the therapy of radiation injury.

III. SCOPE OF THE STUDY

The study was designed to review radiation-induced alterations of gastrointestinal function and metabolism that may permit the development of better methods to treat radiation injury in the soldier. Many recommendations were stimulated by two previous reviews on the immunologic aspects of therapy of radiation injury and the early radiation-induced biological changes that indicate degrees of radiation injury (1, 2). This review included: gastrointestinal symptomatology; immediate post-irradiation cellular events; morphologic responses; gastrointestinal and hematopoietic correlations; intestinal motility and malabsorption; intestinal flora changes; antibiotics in radiation therapy; radiation-induced vomiting; transport of fluid, electrolytes, nutrients, and other essential elements; and alterations in drug metabolism.

The principal concern was to develop guidelines for future research that will be useful in advancing better techniques for treating radiation injury in the soldier. The ideas expressed originated largely from the background of research and experience of the participants and the review and analysis of the problem by the Life Sciences Research Office staff.

The topics selected for review were judged to represent the main stream of work on radiation effects on the gastrointestinal tract. Time may prove that potential opportunities were overlooked, a risk inherent in any analytical review that does not catalog all investigations relevant to the subject.

A critical literature review entitled The Gastrointestinal Syndrome in Acute Radiation Injury and an annotated evaluative bibliography constitute Part II of the report.

IV. AD HOC STUDY GROUP AGENDA

The agenda for the ad hoc study group meeting held at Beaumont, Federation of American Societies for Experimental Biology, Bethesda, Maryland, on September 24 and 25, 1968, included the following topics:

- Gastrointestinal Symptomatology
- Morphologic Response of the Gastrointestinal Tract
- Alterations in the Flora of the Gastrointestinal Tract
- Fluid and Electrolyte Changes in the Small Intestine
- Gastrointestinal Transport of Nutrients and Other Essential Elements
- Gastrointestinal and Hematopoietic Correlations
- Metabolism of Drugs and Their Metabolites
- Antibacterial Agents in Radiation Therapy

V. LIST OF ATTENDEES

AD HOC STUDY GROUP MEETING, SEPTEMBER 24 AND 25, 1968

ON

A STUDY OF THE METABOLIC ASPECTS OF THERAPY OF

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VI. REVIEW DISCUSSIONS

A. GASTROINTESTINAL SYMPTOMATOLOGY

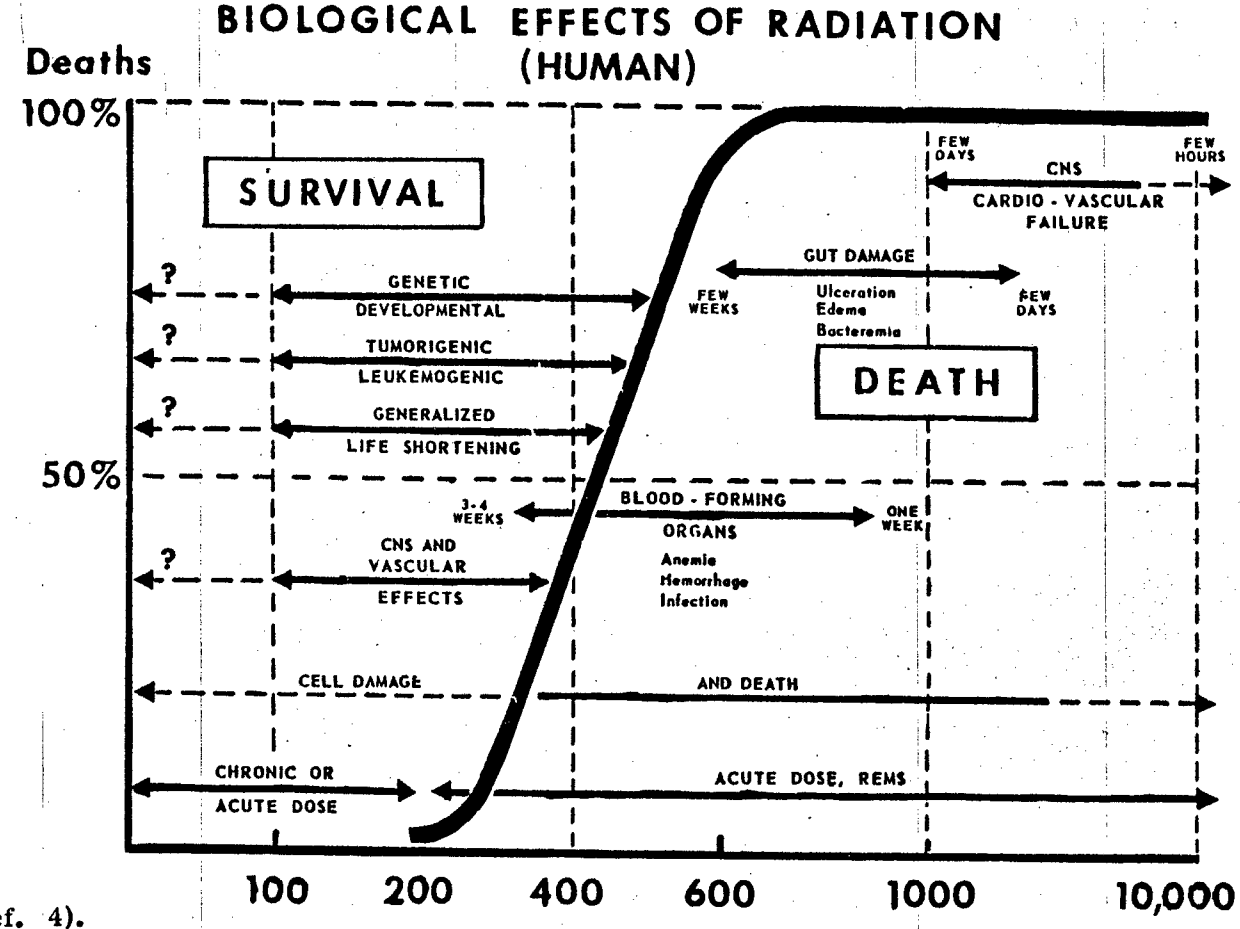
The symptoms characteristic of the radiation syndrome and modes of death attributable to acute radiation injury are generally related to three major tissues: hematopoietic, gastrointestinal, and central nervous system. There is considerable overlap among the syndromes and the treatment regimen is dictated by the presenting symptomatology. The clinical picture following large single or short-term exposures - 24 to 48 hours - includes symptoms referable to hematopoietic depression (<500 to 600 R), gastrointestinal damage (600 to 2,000 R), and central nervous system symptoms (>1,000 to 2,000 R) (Figure 1).

The gastrointestinal symptomatology (See Part II, p 93) apparent soon after radiation exposure is a consequence of injury to two organ systems: the intestinal mucosa and the myelocytic renewal system of bone marrow. To initiate the classical "gastrointestinal syndrome" both organ systems are ordinarily involved and whole-body irradiation is necessary. However, an acute radiation intestinal death may follow irradiation of only the intestine either in situ or exteriorized (5, 6).

Quastler (7) produced an acute intestinal syndrome as evidenced by epithelial loss and death in animals on day 4 or 5 post-irradiation. Loss of the lining epithelium is attributed to inhibition of cell proliferation, presumably in G_2 (See Section VI B, p 26), accompanied by uninterrupted extrusion of epithelial cells at the villus tip. As the time interval between radiation exposure and histologic examination is increased, crypts and villi become progressively shorter.

Initial damage is severe following large doses of whole-body irradiation and recovery of the intestinal epithelium may not occur. Shortened villi covered by degenerating cells are found on histologic examination and death usually occurs in certain species of animals between the third and fifth day without significant regeneration of the small intestinal epithelium.

FIGURE 1



(Ref. 4).

The small intestine is the most radiosensitive portion of the digestive tract and the epithelial cells of the crypt are the most sensitive cells. Thirty minutes after a moderate exposure about half the duodenal crypt cells show nuclear fragmentation, swelling, or other evidence of cellular disintegration (8). Debris accumulates in the crypt lumen and within the first few hours most mitotic activity ceases. After about 24 hours the epithelial surface contains only a single layer of cells and the villi are shortened.

The small intestinal epithelium is approximately as radiosensitive as bone marrow. Stomach and large bowel epithelium are much less sensitive. Blakely (9) intimated, on the basis of data from studies of irradiated animals, that if the patient can be kept alive during the early intestinal phase by fluid and electrolyte replacement, complete reconstitution of the intestinal epithelium may occur. Although the patient may survive the gastrointestinal injury, the effects of severe pancytopenia must be overcome. This has important implications for the medical officer because it may be futile to treat the gastrointestinal injury if the patient is to die from failure of the hematopoietic system.

Bond, Fliedner, and Archambeau (3) concluded that irradiation of the entire bowel is necessary, but not sufficient, to produce the gastrointestinal (G.I.) syndrome. It is clear that the G.I. syndrome and death reflect the synergism of effects of damage to several tissues, principally the gastrointestinal epithelium and the myelocytic renewal system of the bone marrow. It is academic to attempt to differentiate among the several concomitantly developing lethal processes.

The transport of solutes and water by the intestinal mucosa has been the subject of rather extensive study since the latter part of the 19th century (10). In spite of many experiments, the fundamental mechanisms involved in the transport phenomena exhibited by this tissue have remained relatively obscure. More extensive research in this field is urgently required. The effects of radiation exposure should be incorporated in future research on gastrointestinal absorption. It is important not only to investigate "normal" processes and functions, but the opportunity exists to simultaneously study alterations initiated by radiation.

B. IMMEDIATE POST-IRRADIATION CELLULAR EVENTS

The sequence of events following irradiation are dose-related. If the dose is low enough to allow resumption of crypt cell proliferation before death through electrolyte loss, recovery may occur (11). On the other hand, high doses prevent resumption of cell proliferation and death follows. The degree of gastrointestinal injury may be correlated with the generalized symptoms that are produced in the animal or man.

The normal cell population kinetics and the effects of irradiation on the cell population of the intestinal mucosa have been studied extensively. In general, by marking the cells replicating deoxyribonucleic acid (DNA) with a DNA label (tritiated thymidine, ^{3}HTDR) it is possible to study indirectly the processes of proliferation, maturation, movement, and decay in the intestinal crypt. The cell cycle is divided into four phases designated: mitosis (M), post-mitotic (G_1), DNA synthesis (S), and post-synthetic (G_2). Newly replicated DNA can be identified autoradiographically by incorporation of previously injected ^{3}HTDR. This technique provides a useful method for studying kinetics of the gastrointestinal cell system (See Section VIII, p 67).

After whole-body irradiation of the mouse, repair and recovery of the rapidly dividing crypt cells of the intestinal epithelium follows a well defined pattern (12). Mitotic cells are most sensitive; many cells in this stage are unable to complete division and these cells die. Mitosis and DNA synthesis are immediately affected by irradiation. Movement of cells from G_1 into S is retarded or blocked, DNA synthesis is reduced, movement of cells from G_2 into M is also reduced or blocked, and cells in M may have difficulty in completing mitosis (13).

Quastler in his early studies (5) emphasized some limitations of radioactive tracer methodology as applied to the study of gastrointestinal epithelium. Effects of internal radiation of cellular constituents may be observed when doses of ^{3}HTDR are large enough (14, 15). These effects are dose related and high doses of radiation from ^{3}HTDR will severely reduce the crypt cell population (14, 16, 17, 18).

The critical cellular events in the intestinal mucosa of the mouse correlate with the clinical syndrome in man after high doses of whole-body radiation (5, 12). These are outlined as follows:

- Villus cells show little gross change during the first 24 hours;
- Proliferative activity in the crypts is modified during the first, second, and third day; DNA synthesis and mitosis may take place, but viable daughter cells are not produced;
- The crypt cell population is absent by day 3;
- Villus cell population is reduced as a result of the decline in crypt cell population;
- If new cell production is blocked the epithelial mucosa denudes.

For the animal to survive a radiation insult, replacement of the proliferative cell populations is necessary. This may be achieved by an increase in the flow of cells into the maturation and functional phases, that is, an acceleration of cell production rate as suggested by Lajtha and Oliver in 1962 (19). Proliferation, at rates considerably greater than normal, has been demonstrated in the mouse intestinal epithelium after single, whole-body ^{60}Co gamma ray doses (13, 20). The recovery phase involves an increase in the size of the proliferative compartment and an acceleration in the generation cycle. Prior to investigations in vivo (12, 13, 20, 21, 22, 23, 24), concepts of repair and recovery in the intestinal epithelium were based on the study of in vitro cell systems. There is a fundamental difference in the two systems as pointed out by Lesher (12). Cells in vitro do not exhibit the capacity for compensatory acceleration of the generation cycle that contributes to the survival of the animal. In vivo studies are particularly important because they reflect the net effect of various processes that control epithelial cell proliferation in the animal.

(See Section VII, Suggested Areas for Future Research, p 63)

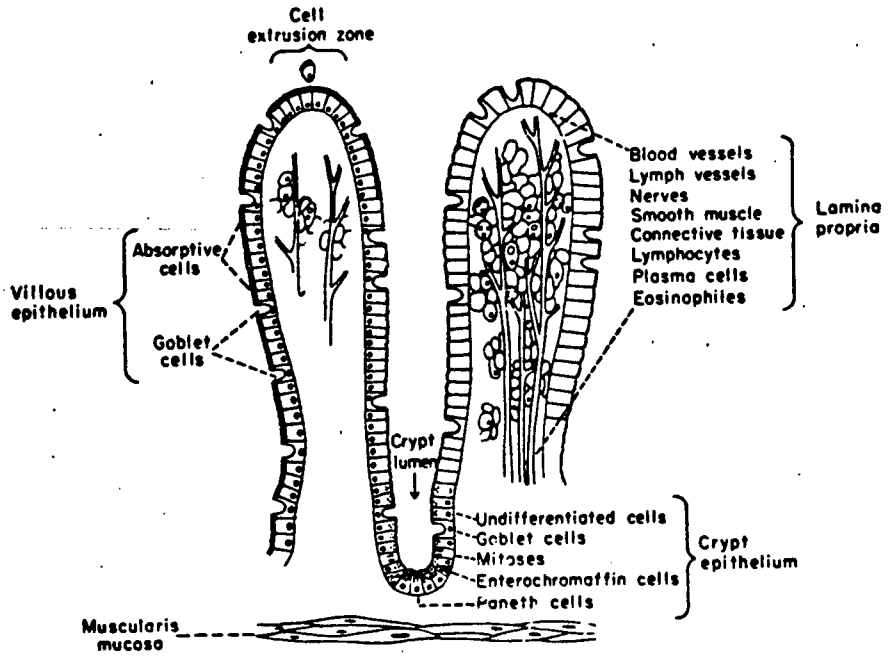
C. MORPHOLOGIC RESPONSES

The normal small intestinal mucosa provides the maximal absorptive surface for the intraluminal contents. Three cell types, the absorptive, the mucous-secreting goblet, and the enterochromaffin cells form the single layer of columnar epithelium which covers the villus (Figures 2 and 3) (25). The luminal surface of the cells is covered by microvilli. The crypt epithelium is characterized by several cell types. The most abundant of these are the undifferentiated cells which may be labeled readily with ^{3}HTDR because these are actively proliferating. Serial duodenal or jejunal biopsies obtained from human subjects permit the study of the morphologic changes in these tissues induced by radiation exposure.

The dynamic nature of the normal cell renewal process in the intestine makes this structure both readily susceptible to radiation injury and rapidly repairable. Essentially complete repair appears to take place if the injury is not too severe. The immediate morphologic response of the mucosa of the human small intestine has been studied in patients receiving therapeutic doses of X-ray (26, 27). These patients received skin doses of 150 to 300 R for 5 to 6 days per week for two to four weeks and they remained essentially free from clinical symptoms that could be attributed to irradiation therapy. Light and electron microscopy of biopsy histologic sections revealed a 25 to 51% reduction in mitosis with a marked shortening of the villi and a reduction of epithelial surface (Figure 4) (25). Giant epithelial cell forms and a heavy infiltration of the lamina propria with plasma cells and polymorphonuclear leukocytes were observed. Biopsies from the small bowel outside the field of irradiation appeared normal. This finding suggests that the radiation-induced mucosal lesions were limited to the area directly exposed to irradiation. The histologic changes observed were similar to those found in the small intestine of laboratory animals after exposure to sublethal doses of irradiation.

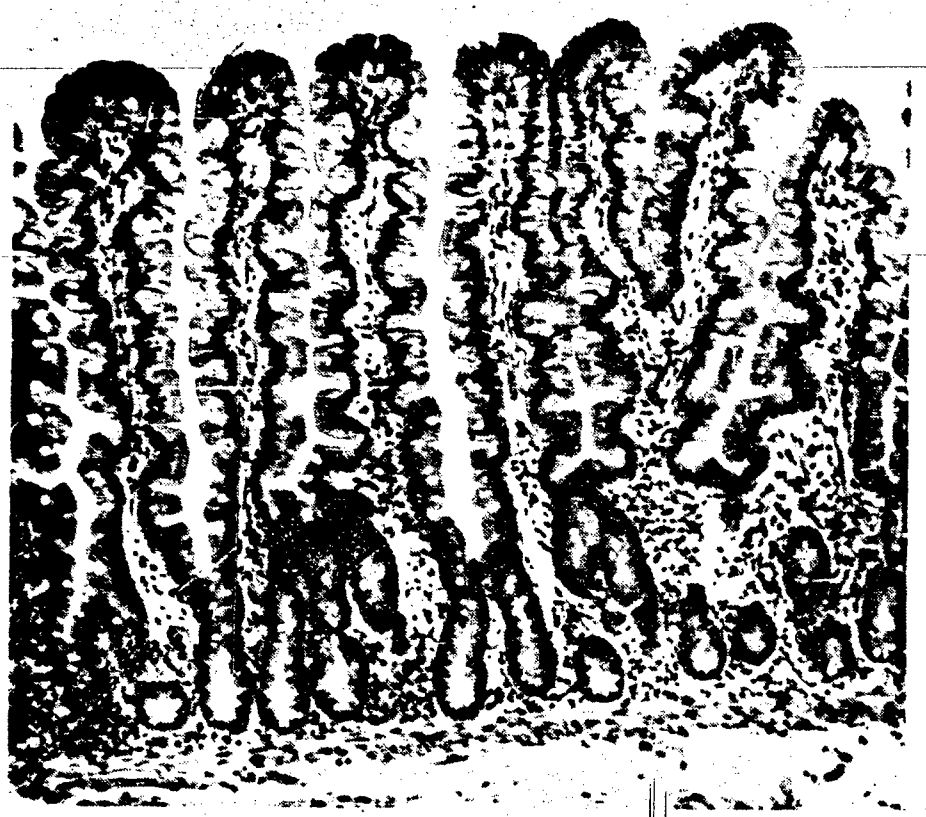
The findings in the small intestine were confirmed for rectal tissue in somewhat similar studies in patients receiving pelvic X-ray therapy for malignancies (28). In one study of eleven patients, symptoms, sigmoidoscopic findings, and histological and histochemical changes in the rectal mucosa were evaluated at 0, 10 and 20 days

FIGURE 2



Schematic diagram of 2 villi and a crypt to illustrate the histological organization of the mucosa of the small intestine (Courtesy J. S. Trier; Ref. 25).

FIGURE 3



Light micrograph of a section of jejunal mucosa obtained by peroral biopsy from a normal adult. X 150 (Courtesy J. S. Trier; Ref. 25).

FIGURE 4

Representative sections of three biopsies from a patient undergoing X-ray therapy. A: Before treatment. The biopsy appears normal. X 75. B: After 3,000 roentgens. Both crypts and villi are shorter than normal, resulting in a distinct decrease in mucosal thickness. There is also increased infiltration of the lamina propria. X 75. C: Two weeks after cessation of X-ray therapy. Jejunal morphology has reverted to normal. X 75 (Courtesy J.S. Trier; Ref. 25).

during the course of radiation treatment. The total radiation doses ranged from 4,000 to 6,000 rad delivered over various time periods from 28 to 62 days. The rectal mucosa in biopsy specimens during X-ray treatment was abnormal in every case. Leukocytic infiltration of the lamina propria and dysplasia of the superficial and crypt epithelium were characteristic findings. Prominent tissue eosinophilia was noted and eosinophilic crypt abscesses were observed in 9 patients. The marked tissue eosinophilia was considered nonspecific. The radiation-induced histologic changes in the muscularis mucosa, lamina propria, and glandular and surface epithelia returned to normal within one month. Apparently the rectal mucosa responds to radiation injury in a manner that resembles the recovery of the villous epithelium of the small intestine.

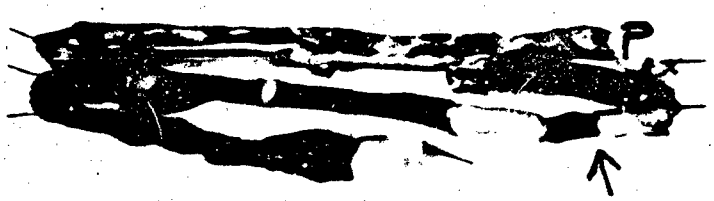
The rate of cell turnover of the small intestinal epithelium of man is rapid. As measured by the migration of ^{3}HTDR labeled crypt cells, complete replacement of the villous epithelium occurs in 5 to 6 days. Radiation inhibits cell division, causes a reduction in cell turnover, and induces morphologic changes as described previously. Many workers have observed the relatively prompt and complete recovery of these mucosal lesions after radiation. Indeed, mitotic events appear normal within 3 days and normal villi are found in biopsy sections within two weeks. Rectal mucosa also shows great capacity for recovery from radiation injury. In studies on therapeutic irradiation of the abdomen of human patients, it is essentially impossible to determine accurately the dose to particular segments of the gastrointestinal tract. There may be significant differences in the extent of radiation received by the small intestine as compared with the large intestine, because of anatomic and physiologic differences.

In studies on patients receiving post-operative irradiation for carcinoma of the stomach, biopsies revealed that the villi of the human jejunal mucosa becomes progressively shorter following therapeutic irradiation until villus structure is unrecognizable and the mucosal surface appears flat (29). Recovery may take place rapidly, the mucosa forming convoluted and folded villous ridges instead of finger-like villi. The biopsies revealed also that the mucosa reached an equilibrium about one month after completion of the radiation treatment and no further material changes in the mucosa were noted up to six months after the radiation therapy was terminated.

Rats whose exteriorized intestines have been irradiated with 2,000 R X-rays, offer a useful model to study the development and repair of mucosal radiation lesions of various severity (6, 11, 30). The uniform classic lesion of the acute intestinal radiation syndrome described after whole-body irradiation of the intact rat was not observed. Three days after exposure, the exteriorized, irradiated intestine exhibited a discontinuous pattern of patchy lesions alternating with areas with well formed villi (Figures 5, 6, and 7). In the injured areas the mucosa showed short, stubby villi or was avillous. There was no denudation, but the mucosal surface was lined by a continuous layer of large foamy epithelial cells. The characteristic vacuolization of these cells was due to the presence of many, large lipid droplets. Later, focal erosions and ulcers of various size were observed occasionally. These were characterized by an inflammatory response in the immediate region and by hemorrhages and cellular exudate. The discontinuous nature of the radiation-induced lesions in various regions of the exteriorized small intestine could not be explained; certain areas appeared to be protected from the full effect of irradiation. It was suggested that some interference with the blood supply to these areas, possibly related to the process involved in exteriorizing the gut, could produce the effects observed.

(See Section VII, Suggested Areas for Future Research, p 63)

FIGURE 5



Intestine obtained 5 days after irradiation has been processed for the demonstration of alkaline phosphatase. In the normal rat there is a decreasing gradient in the activity of this enzyme from the pylorus (P) to the ileum and this gradient is reflected in a different coloration of the villous areas, moderately dark in the jejunum and lighter in the ileum. In this specimen the avillous areas have reacted intensely due to the diffuse activity in the lamina and in the numerous neutrophils. The area indicated by the arrow is magnified in Figure 6. (Courtesy Helen R. Jervis; Ref. 11).

FIGURE 6

A higher magnification view of that part of the ileum indicated by an arrow in Figure 5. It shows the characteristic ridge-like villi of the adult rat, next to an avillous area (Courtesy Helen R. Jervis; Ref. 30).

FIGURE 7

Histologic section of specimen illustrated in Figure 6. Notice the abnormal length of the villi on the right and the complete villous atrophy on the left. Characteristic of the atrophic areas, in the rat, are the cystic crypts. Even within such extremely injured areas clonal crypt regeneration is apparent. In this preparation the epithelial covering is missing, so the mucosa could be considered as denuded. This denudation, however, is an artifact due to excessive handling before embedding (Courtesy Helen R. Jervis; Ref. 30).

D. GASTROINTESTINAL AND HEMATOPOIETIC CORRELATIONS

The sequence of events following single or short-term exposures to penetrating radiation have been described as these relate to the hematopoietic and gastrointestinal systems (3, 5, 31). Hematopoietic tissue injury is important in causing death of animals developing the gastrointestinal syndrome because:

- The gastrointestinal epithelium is lost or is spread extremely thin to cover the flattened villi;
- The thin or absent epithelial covering results in increased likelihood of intestinal breaks or ulcerations through which bacteria or toxic materials may enter the circulation;
- Severe granulocytopenia results with a reduced number of circulating or tissue granulocytes or monocytes to combat infection;
- Few or no lymphocytes are present in intestinal lymphoid tissue to produce antibodies locally. Severe thrombocytopenia greatly increases the likelihood of uncontrolled bleeding from lesions in the gastrointestinal tract; and
- With large numbers of bacteria released into the circulation and the presence of increased capillary permeability and fragility and thrombocytopenia, the bacteria leave the circulation and establish fulminating infections.

Thus, there is a close association between the functional efficiency of the gastrointestinal and hematopoietic systems and the development of the full radiation syndrome.

Attempts have been made to compute the rates of cell turnover in these two systems to correlate their relative degree of radiation susceptibility. It was calculated that while the life span of red blood cells in man is about 4 months, the corresponding turnover of

epithelial cells of the small intestine is approximately fifty times as fast. The life span of these latter cells is only two to three days. The activity of these two proliferating systems and the white blood cells provides a partial explanation of their relative vulnerability to radiation. In addition, the radiosensitivity of the myelocytes, lymphocytes, and testicular cells is probably due to their rapid proliferation rates.

The relative "radiosensitivities" of the intestinal epithelium and the bone marrow are difficult to assess. Dose-effect curves have been developed for bone marrow stem cells and intestinal epithelial cells. The D_0 values, reflecting the slopes on the exponential portion of the curves, are similar. In this sense, the two cellular systems are approximately equally radiosensitive. On the other hand, the shoulder on the curve for intestinal epithelial cells is broader than for bone marrow stem cells. This probably reflects a greater recovery capability in the cells of the intestine than in the cells of the bone marrow. Thus, to reduce the number of intestinal epithelial cells to approximately 1% of their original number, the radiation dose necessary is greater than for bone marrow stem cells. Clinically, therefore, the shoulder region of the dose-effect curve is probably a better index of radiosensitivity than the slope of the exponential part of the curve at high doses.

In contrasting the cells of the two systems and their response to radiation, it has been noted that the hematopoietic cells depend upon the cortical bony medulla for successful bone marrow grafts. On the other hand, the epithelial cells of the intestine appear to continue to produce crypt cells without a sustaining tissue environment. For successful intestinal epithelial cell propagation in vitro, an organ culture system is required which includes, in addition to the epithelium, the basement membrane and lamina propria (32). For example, bone marrow transplants continue to produce viable hematopoietic elements indefinitely when transferred to other tissues in the body as long as bony medulla is also transferred. Within a few weeks cellular hematopoietic marrow is regenerating and apparently functioning cells are produced (33). Presumably, after irradiation it is important to consider not only survival of the marrow cells but also survival of bony medulla. It is known that marrow cells and bony medullary tissue exhibit a preferential sensitivity to varying doses of radiation. Radiation exposure sufficient to destroy bony medulla renders the animal or man unsalvageable. There may be a funda-

mental difference between restoring bone marrow and restoring the gastrointestinal epithelium after radiation injury.

Relatively few hematopoietic stem cells, even in a localized area, may be adequate to repopulate hematopoietic tissue so long as the tissue architecture is not irreversibly damaged or altered by doses of ≈ 1,000 R. There is no evidence that a similarly small number of crypt cells in a localized area of the gastrointestinal tract would be equally effective in repopulating the entire intestinal epithelium. On the other hand, relatively few surviving crypt cells in each of many widely distributed crypts can undergo rapid proliferation and lead to regeneration of epithelium if the irradiated animal can be kept alive. Expressed in another way, if the structural integrity of the two components of the intestinal mucosa, the epithelium and the lamina propria, is preserved, renewal and regeneration of the functioning cells are possible. The mesenchymal cells of the lamina propria have their own type of cell renewal and turnover (32).

Other factors are significant in the regeneration phenomena. These are motility and tonus of the intestinal tract, microcirculation, local immune systems, and metabolic mechanisms. These are all influenced by radiation.

(See Section VII, Suggested Areas for Future Research, p 64)

E. INTESTINAL MOTILITY AND MALABSORPTION

The physiological processes that result in the movement of a dietary constituent from the bowel lumen to the blood or lymph are complex and may be altered by irradiation. Ingelfinger (34) noted that intestinal absorption in its narrowest sense is the passage of a substance from the intestinal lumen to the inside of the mucosal epithelial cell. In its broadest sense, intestinal absorption encompasses the whole sequence of events between the introduction of a substance into the intestine and its eventual appearance, in original or derivative form, in portal blood or mesenteric lymph. Laster and Ingelfinger (35) tabulated these factors as follows:

- Intraluminal digestion;
- Binding of the substance to be absorbed to the surface of the intestinal columnar cell;
- Transport across the luminal surface of the columnar cell membrane;
- Intracellular metabolism and transcellular transport;
- Release from the cell;
- Migration across the basement membrane of the musocal epithelium and through the lamina propria; and
- Penetration into blood or lymph capillaries.

This description of the physiology of intestinal absorption reflects the complexity of the system itself and the several interactions that occur between different absorbed nutrients. The intestine is a transporting organ with a multi-layered barrier composed of at least two plasma membranes, an external mucopolysaccharide coat, and an internal cellular pathway containing mitochondria, endoplasmic reticulum, a Golgi complex, vesicles, a nucleus, and other subcellular organelles (36). Each of these intracellular entities may have a central role in the absorption process by supplying energy and enzyme systems, serving as

intracellular channels, or as the site of genetic information that may modify the efficiency of the process.

Digestive processes precede absorption; the long-range transport systems of blood and lymph become important after absorption. The rapid absorption of orally administered drugs usually depends upon their swift transfer to the small intestine. Here the specialized nature of the mucosa and the large surface area relative to the volume of the luminal contents favor absorption (37). Means of hastening, or slowing, gastric emptying are therefore of interest in practical therapeutics. The rate of gastric emptying is dependent upon a balance between gastric distention promoting emptying and stimuli acting in the intestine to depress emptying; both may be affected by irradiation. The oral therapeutic route may be contraindicated in patients suffering radiation injury, especially whole-body exposure to doses in the range > 150 to 200 rad where symptoms of nausea, vomiting, diarrhea, decreased motility, and mucosal damage are prevalent.

Ionizing radiation damages the basic intestinal functions of secretion, motility, and absorption. Changes in intestinal motility (38) and absorption (30, 36, 39) may be observed immediately after irradiation. Intestinal absorption of a variety of substances may be either increased or diminished following radiation of the whole body, the abdomen alone, or the exteriorized intestine. A malabsorption syndrome may follow exposure to radiation (39). The response depends on the amount of radiation administered and individual tissue sensitivity. Factors which may lead to malabsorption include impaired epithelial cell production, fibrous replacement of the muscularis, or thickening of the blood vessels within the submucosa.

Radiation-depressed intestinal motility in the rabbit was prevented by continuous infusion of serotonin (5-hydroxytryptamine, 5-HT), but the medication was ineffective if administered by a single injection (38). Motility depression by radiation was thought to be mediated by an excessive release of 5-HT from the intestine and constantly released 5-HT plays a role in normal physiologic intestinal motility. The major storage sites for 5-HT in mammals are the enterochromaffin cells of the gastrointestinal mucosa. Reserpine, a 5-HT releaser, inhibited motility to a considerable degree, and ether and pentobarbital (thought to liberate 5-HT from the intestine) produced temporary depression of intestinal motility. Kagnoff

and Kivy-Rosenberg (40) demonstrated that only drugs which act on neurohumoral components or neural elements within the small intestine result in peristalsis contraction patterns in jejunal segments of nonirradiated rats mimicking the pattern observed in irradiated animals. Since the radiation-induced response could not be mimicked entirely by a single class of drugs, the authors proposed that the radiation damage is located at more than one of these areas.

A recent review (2) emphasized that reports of radiation-induced changes in detoxification enzymes, drug metabolism, and biochemical parameters were contradictory and inconclusive. Similarly, Duncan and Leonard (41) reviewed the literature (through 1965) and were able to find only five examples, in addition to their own, of an established malabsorption syndrome following therapy. The intestine is often unavoidably irradiated during radiotherapy and its tolerance is recognized as the limiting factor in treatment. Dobbs and Webster (42) reported the earliest clinical observations on malabsorption following radiotherapy to the abdomen as increased fat excretion in the feces. Four recognizable syndromes are evident if the small intestine is damaged by radiotherapy: acute necrotizing enteritis, subacute segmental enteritis, chronic enteritis, and intestinal stenosis (41). Malabsorption may occur with each syndrome and sometimes may be the predominant feature. In three patients undergoing radiotherapy for pelvic tumors, all developed diarrhea following the initial treatment, progressing a few weeks later into symptoms of subacute obstruction with colic and abdominal distention. In addition, all three exhibited some form of malabsorption: two showing increased fat excretion and one decreased absorption of vitamin B_{12} (43).

Commonly prescribed drugs are used in treating the symptoms of radiation injury. However, because the intestinal system is altered structurally as well as functionally, malabsorption should be expected to modify the pharmacologic effects. Whether or not drugs administered during this period will be absorbed normally is not known.

The majority of studies of radiation-induced gastrointestinal symptomatology pertain to small animals. There is an urgent need for controlled studies in higher mammals before meaningful information can be obtained that will allow better drug treatment of the irradiated human.
(See Section VII, Suggested Areas for Future Research, p 64)

F. INTESTINAL FLORA CHANGES

Following high-dose, whole-body radiation, the gastrointestinal epithelium is severely damaged and areas of ulceration permit bacteria from the lumen to diffuse to the underlying tissues. Any abnormality of the small intestine which interferes with orderly intestinal peristalsis and allows stasis of intestinal contents eventually results in intraluminal bacterial overgrowth (44). This does not necessarily mean that infections from virulent bacterial pathogens will appear. However, overgrowth of normal flora may give rise to opportunistic infections (1). The term "opportunistic pathogen" may be applied to those microorganisms that are of limited virulence for normal man, but that may readily invade, multiply, and produce disease in patients who have underlying conditions that decrease resistance to infection (45). Granulocytopenia, reflecting serious infection by enteric bacteria, often occurs in patients with neoplastic diseases who are treated with X-ray therapy or bone marrow suppressants and, in general, in any victim of an accidental radiation exposure. The rapid overgrowth of normal gastrointestinal flora could easily disrupt absorption patterns and kinetics. The result could increase the detrimental effects of diarrhea.

Normally, the resident bacterial population of the human jejunum is sparse, but when intestinal transit is retarded by motor dysfunction and obstructing lesions, microorganisms become prevalent in the upper small intestine (46). This condition will occur following high-dose whole-body radiation exposure (47).

Excessive numbers of small bowel microorganisms not only metabolize nutrients that are "left over" because the patient cannot absorb them, but also these organisms sometimes preempt, for their own use, essential dietary factors (46). In any absorptive disorder, unabsorbed nutrients reach the bacteria-rich lower intestine where they provide substrate for bacterial growth.

Fordtran (48) defines diarrhea as water and electrolyte malabsorption. Radiation-induced diarrhea, coupled with severe vomiting episodes, contributes to excessive bacterial overgrowth of both pathogenic and nonpathogenic organisms. Four theoretical mechanisms have been proposed as the probable etiology of patho-

genic bacterial diarrhea (48): interruption of normal mucosal cell transport process; deranged intestinal permeability; the presence in the intestinal lumen of unusual amounts of nonabsorbable, osmotically active substances; and finally, abnormal intestinal motility. All of these mechanisms, either alone or in combination, may contribute to radiation-induced diarrhea. They may produce local effects in addition to the possible central nervous system action that actively stimulates vomiting. Metabolites resulting from bacterial utilization of unabsorbed sugars produce cramps, gas, and loose, frothy stools (46). Bacterial metabolites of these unabsorbed nutrients may be absorbed also and excreted in the urine (44).

(See Section VII, Suggested Areas for Future Research, p 64)

G. ANTIBIOTICS IN RADIATION THERAPY

Atrophy of the villi occurring in the small intestine after whole-body irradiation is usually repaired, and seldom results in chronic changes if the patient lives. Infection often plays a major role in the gastrointestinal syndrome. Commensal bacteria within the intestine may exert adverse effects on cells and villi, although this has not been proved (49).

Excess bacterial toxins produced following irradiation may have easier ingress through the injured intestine (50). These effects appear to be less important in the response to the usual form of radiotherapy than in the gastrointestinal syndrome.

Clinically, antibiotics have been used to control infections following radiation injury; however, their use may disturb the normal intestinal flora and produce adverse effects. It is recognized that the destruction of a large number of bacteria may release endotoxins in amounts that may be fatal to an irradiated animal or man. This appears to be the explanation for the sudden death that may occur when irradiated animals are treated exceptionally vigorously with antibiotics at a time when they are highly susceptible to endotoxin shock. In cases of this type, antibiotic therapy should be administered with great caution (1).

With gradually increasing doses of radiation therapy, chronic arteritis and ulceration are produced following large total dosages. Infection has been shown to be an integral part of the ulceration. Bacterial growth is visible at the damaged mucosal surfaces or sometimes in the deeper parts of the mucosa, and it has been postulated that infection by these organisms may help to initiate or accompany ulceration. In a few instances, bacteremia induced by the normal flora of the intestine has been observed. Infection in radiation therapy is a factor in ulceration, perforation, local fistula, and abscess formation.

The clinical implications of intestinal infection following radiotherapy were studied in patients with carcinoma of the cervix (51). The complications were recorded according to severity and antibiotics were not normally administered prophylactically, although they were employed in a few patients who developed perforation with localized peritonitis or abscess. Patients with frank

ulcerative colitis or rectosigmoiditis showed no instances of bacteremia. In the treatment of malignant testicular tumors and lymphomas, including irradiation of the small intestine, in which considerable evidence of enteric toxicity was encountered, no definitive evidence of bacterial infection as a major factor in therapy occurred (52). In the majority of patients in both these studies, symptomatic treatment of nausea and diarrhea was indicated. The complications of structure, obstruction, and perforation appear to be caused by the radiation-induced pathology, and infection probably played a minor role.

The empirical use of antibiotics in radiation-induced ulcerative intestinal injury, in the hope of accelerating healing or preventing complications such as infectious perforation, is open to question. Antibiotics following perforation and abscess formation may, of course, be life-saving (53). Clinically, therefore, it is questionable if "prophylactic" antibiotics administered during radiation therapy are valuable.

Suggested future investigations to resolve the question of bacterial invasion during radiation therapy might include controlled studies on patients with enteric radiation injury. Frequent blood cultures following therapeutic radiation may be used to estimate: the frequency with which small numbers of organisms are released into the circulation; the rate at which they are cleared; and the frequency of septicemia, pyleonephritis, or remote abscess formation in patients or animals when showers of bacteria are released.

(See Section VII, Suggested Areas for Future Research, p 65)

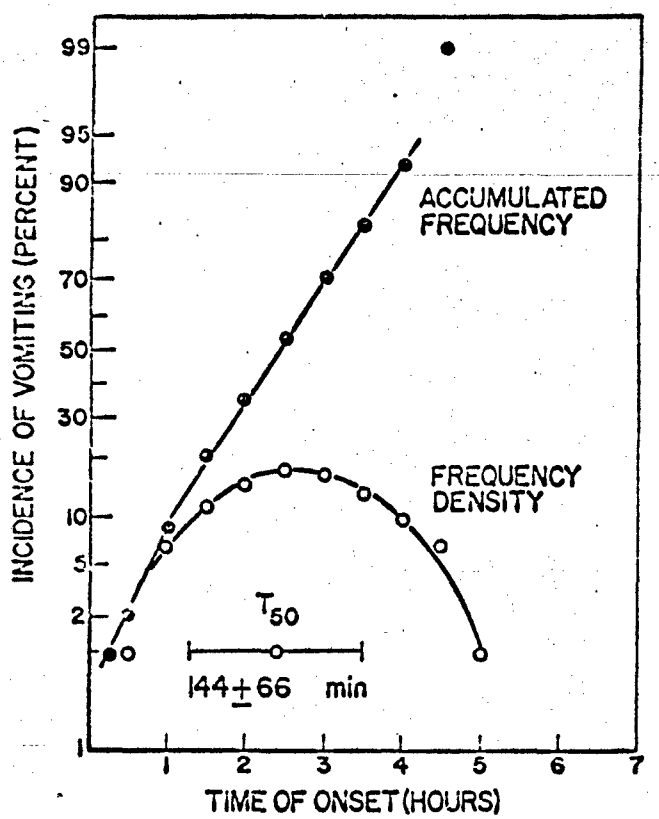
H. RADIATION-INDUCED VOMITING

Vomiting is important as a clinical symptom of radiation exposure and as a manifestation of the gastrointestinal syndrome. Numerous drugs are used in the treatment of radiation nausea and emesis (54). Following radiation exposure, vomiting in man is virtually certain to occur at doses > 200 rad (2). In animal radiation studies, vomiting is a prominent early symptom. For example, of 66 monkeys exposed to gamma-neutron radiation (336 to 528 rad, midline tissue dose), 79% vomited within 2 hours after irradiation; a majority of these episodes occurred between 30 and 60 minutes post-irradiation (55). The vomiting incidence during the first 2 hours did not vary greatly between eventual survivors (76%) and decedents (80%). Beagles exposed to midline tissue doses of X-rays (175 to 271 rad) or mixed gamma-neutron radiations (166 to 292 rad) were observed hourly for vomiting during the first day post-irradiation (56). Occurrence or frequency of vomiting between survivors and decedents were not significantly different. The survivor group had the lowest incidence (30%) of vomiting. Emesis was noted in 50 to 90% of the dogs in groups where deaths occurred. Vomiting episodes were observed throughout the 24-hour observation period, but 30% occurred within 2 to 4 hours post-irradiation. Two-thirds of the animals that vomited had done so at least once within the first 4 hours after exposure. In these investigations vomiting was not dose dependent.

Prominent gross pathological lesions found in decedents, in the monkey studies (56), included hemorrhages in most organs and tissues, pneumonia, peritonitis, pleural adhesions, intestinal adhesions, ulcers and erosions of the large intestinal mucosa, and hyperemia of the kidneys. The ulcerations of the colon were usually deep into the muscle layers. Hemorrhage of the gastrointestinal tract was commonly found with little or no relation to the dose. Other gastrointestinal lesions including peritonitis, ulceration, and adhesions were observed also in all dose groups.

The time of onset of potentially debilitating reactions such as nausea and vomiting is quite important (57). The prodromal responses that would be expected to influence performance significantly are nausea and vomiting. The anticipated vomiting incidence in men exposed to single high-intensity radiation doses (> LD_{50} for man) is depicted in Figure 8. Gerstner (58) predicted the peak occurrence of these symptoms, if at all, singly or together, to be about 5 to 6

FIGURE 8



Anticipated elapsed time between irradiation and onset of severe nausea and vomiting in a sample of 100 persons exposed to radiation doses in the lethal range. (Reprinted with permission from Ref. 57).

hours post-irradiation. Figure 8 also estimates the 50th percentile (T_{50}) of men laboring to continue a high performance level.

Local gastrointestinal pathological conditions assume a significant role in the general health and probable survival of the irradiated animal or man. Whether radiation-induced emesis results from a direct or indirect effect on the central nervous system and/or is confined to a local gastrointestinal disturbance remains a moot question (see Appendix, p 67). In either event, research studies to explore and categorize radiation-induced emesis may be expected to yield methods for modifying or abolishing this symptom in some situations and should be encouraged.

(See Section VII, Suggested Areas for Future Research, p 65)

I. TRANSPORT OF FLUIDS, ELECTROLYTES, NUTRIENTS, AND OTHER ESSENTIAL ELEMENTS

Ionizing radiation depresses the active processes of fluid and electrolyte transport in the small intestine but the sequence of events that lead to this depression of absorption have not been established. Although the pathways of movement of essential electrolytes, water, and un-ionized substances from the lumen of the intestine by the epithelial cells and the associated structures to the blood and lymph have been studied in detail, the physiological and biochemical mechanisms are not entirely understood. The study of the effects of radiation on these processes has led to a better understanding of the mechanisms involved and offer approaches to the treatment of the effects of radiation. This subject has been reviewed (3, 31).

In general, the loss of water and electrolytes that follows exposure of the intestine to radiation doses exceeding 1,000 R is an important contributory cause of death in the early post-irradiation period. Nutrients such as glucose (59), thiamine (60), and pyridoxine (61) are not absorbed normally in the immediate post-irradiation period. However, there is little, if any, basic impairment in the absorption of fat or protein in irradiated mice during the first 4 days after exposure and no major absorption differences in the absorption of palmitic acid or glyceryl tripalmitate could be demonstrated in mice receiving supralethal doses of X-rays (62). Following radiation injury sufficiently damaging to cause the loss of functioning mucosa, cyanocobalamin (vitamin B_{12}) is not absorbed in normal amounts. However, the absorption of B_{12} was not reduced during the first 24 hours after irradiation (63).

The changes in body fluid and electrolytes, notably body sodium, are minimal until all the epithelial cells that were present on the villi at the time of irradiation have been substituted on the mucosal surface by the abnormal cells formed in the crypts after irradiation (64). This is a time-related phenomenon and coincides approximately with the onset of diarrhea. Thus, the body water and blood volume during the first 2 to 3 days following exposure to high doses are not significantly changed from normal values.

The mechanisms associated with post-irradiation diarrhea are the subject of controversy. Some workers contend that the diarrhea is related to failure of intestinal absorption and an increased

loss of water into the intestinal lumen accompanied by marked dehydration of the tissues. However, mice or rats may appear normal for 3 to 4 days after lethal doses of radiation and then in a matter of a few hours rapidly become moribund. It is speculated that the animal remains relatively well as long as the epithelial cell barrier between the lumen of the bowel and the tissues remains intact. As soon as this barrier loses its integrity infection and fluid and electrolyte imbalance follows (3, 65, 66, 67).

Other investigators do not interpret their results as a dehydration phenomenon and point out that body water loss 4 days post-irradiation is minimal. Some animals show a net gain in total body water when fluid intake and excreted water are measured. Using ^{22}Na in normal animals to measure the body sodium electrolyte pool it is possible to balance input and output in a steady state. If experimental animals injected with ^{22}Na are starved, the output of sodium decreases and compensatory sodium retention occurs. Starved or pair-fed control animals should show the same degree of retention of ^{22}Na if normal homeostatic water mechanisms are operative. If radiation altered these mechanisms, or caused a leak in the system as is expected after loss of intestinal epithelium, the irradiated animal should be unable to conserve electrolytes. The results showed the whole-body sodium turnover and decrease in exchangeable sodium mass were essentially alike in starved rats after 700 R exposure (hematopoietic syndrome), and starved rats after 2,100 R exposure (gastrointestinal syndrome). Experiments with ^{42}K or ^{3}H water labels in other animals have produced results similar to those obtained with ^{22}Na balance studies. The inability of parenterally administered fluids or electrolytes to prolong life or prevent death of animals after such doses of irradiation supports the nondehydration hypothesis (65, 66, 68).

These experimental studies are discussed in two recent symposia (31, 67). The matter is obviously not settled and additional investigations are required to understand the finer mechanisms of cell injury that control the transport of fluid and electrolytes.

Malabsorption of fats, sugars, iron, and vitamin B_{12} has been studied in patients undergoing abdominal radiation therapy (69). Although the decreased absorption of these substances was not correlated with the dose of radiation administered, in general, the effects observed in patients were similar to those found in animal

studies. However, Donati et al. (30) reported an increased rate of intestinal absorption of radio iron following X-irradiation of the exteriorized small intestine of the rat.

Ligation of the bile duct or cannulation and diversion of bile will prevent diarrhea in the irradiated rat (3, 70). In the investigation of the mechanisms by which bile salts cause diarrhea in irradiated rats, the function and transport of water and sodium was measured in situ in the small and large intestine (71). Impaired reabsorption of fluid and electrolytes appears to be the cause for the loss of these substances rather than increased exsorption; the exclusion of bile results in improved reabsorption.

In the studies by Sullivan and associates (70, 71) of the critical function of sodium transport, as influenced by low-sodium diets, excessive NaCl diets and in situ perfusion of the intestine in rats receiving 1,000, 1,300, or 1,400 R doses, it was found that essentially no sodium was lost until the third day by animals on the low sodium diet. As detected by ^{22}Na, the presumed similar loss of sodium by rats on the high-sodium diet was masked by the high excretion of sodium by these animals. The total loss of sodium by the low-sodium diet animals was 23%. This quantity of sodium loss may be sufficient to cause death of the rat. In insorption studies (passage of ^{22}Na- and ^{3}H-labelled buffer out of the intestine) and exsorption studies (movement of an intravenously injected label into unlabelled buffer perfused through the lumen), irradiation decreased both insorption and exsorption. Bile duct cannulation, to divert the bile, prevented the effects of radiation on water and sodium transport. Thus, it does not appear that sodium loss is the critical event that causes the death of the irradiated animal.

To measure the net change in fluid and electrolytes in the irradiated rat, the small intestine was ligated at both pyloric and ileocecal junctions. Labelled buffer was injected into the lumen and the amount exchanged in 30 minutes after radiation was measured. Control animals received the label by injection into the blood and similar analyses of the lumenal contents were made. By these tests, radiation decreased the insorption of sodium and potassium. Bile diversion prevented the effect of radiation on sodium insorption but not potassium movement. The major cause of accumulation of sodium in the lumen of the intestine after irradiation was demonstrated by the rate of appearance of radioactivity in the lumen after intravenous

injection of the labelled compounds. The degree of injury to the absorptive process determines the amount of sodium accumulation within the lumen of the intestine. Sodium accumulation continues following irradiation, while in unirradiated rats or rats with bile fistulas the process rapidly reaches equilibrium. It was concluded that irradiation causes sodium loss initially by inhibiting the reabsorption of secretions of the small intestine. The accumulation of these secretions including the bile, stimulates additional movement of electrolytes and fluid into the lumen, increasing motility of the intestine and provoking diarrhea.

Nutrient absorption has been studied using isolated, exteriorized intestinal segments and intact sections of the irradiated small intestine. Active transport (thiamine and glucose) and passive transport (xylose) are maximally inhibited 3 days after moderate whole-body radiation (8). Rapid cessation in the active transport of sodium and water as well as absorption defects were noted for pyridoxine and oleic acid, but not corn oil (3). Lipid absorption is essentially unaltered, but steatorrhea persists. Appearance of new, abnormal, epithelial villi cells approximately 3 days after exposure correlates well with the peak maltransport phenomena. The subsequent mitochondrial swelling and loss in the intestinal epithelial cells signals the later decrease in transport function of the intestine during the second week post-irradiation.

If the effects of ionizing radiations per se are to be studied, the only valid biochemical observations, according to Bacq and Alexander (72), are those made within a few hours post-irradiation. A number of convincing reasons are enumerated in support of this hypothesis. For example, the fundamental primary chemical changes always precede the appearance of anatomically visible lesions. Biochemical investigation immediately after irradiation is advantageous because the animals (and men) are still in good condition, suffering neither from shock (except man), infection, nor from severe malnutrition caused by vomiting, anorexia, and diarrhea. These symptoms when manifest after several hours will obscure the accuracy of the biochemical measurements because secondary alterations will have been produced.

Reduced intestinal absorption of all substances at doses approaching the $LD_{50/30}$ days and higher reach maximum malabsorption between days 2 and 3. In spite of the precarious anatomical condition of the intestine, carbohydrates, fats, and proteins

are still absorbed. The observed disturbances are of a trivial type and can be often regarded as secondary to anorexia and diarrhea, vomiting, or disturbances in capillary permeability. Recovery during the first 7 days following all doses of radiation, parallels that for cell loss and regeneration of the intestinal epithelium. Defects in the transport of nutrients and other essential elements across the gastrointestinal barriers, are, in general, considered to be a consequence of cell loss or possible morphologic or genetic abnormalities in the replacement cells (3, 72).

(See Section VII, Suggested Areas for Future Research, p 65)

J. ALTERATIONS IN DRUG METABOLISM

Metabolic alterations induced by radiation on the processes of absorption, distribution, and excretion of drugs and other substances may be of paramount importance in radiation injury therapy. Data on the fate of drugs in the post-irradiation state are scarce. Similarly, alternate mechanisms of action and/or routes of biotransformation may occur if the irradiated individual experiences decreased liver and kidney function and similar changes in other excretory and detoxifying mechanisms.

Drug therapy for the treatment of radiation-induced symptomatology has been based on the assumption that the expected clinical responses to the drugs are unaltered. Evidence from radiation accidents involving men and from animal investigations indicates that this assumption may not be valid for all drugs (73).

The possibility of the soldier receiving multiple traumatic injuries in addition to radiation exposure in the event of a nuclear incident is indeed high. Therefore, the administration of various agents, for example, anesthetics and antibiotics, would be used to aid in diagnosis and treatment. Thus, it is important to know whether these agents would exhibit any untoward effects.

Drug absorption across the biological membranes of the gastrointestinal tract is particularly important. The effects of radiation on intestinal absorption of sugars, fats, electrolytes and water, and vitamin A has been reviewed (74).

Biopharmaceutical parameters such as disintegration time, dissolution rate, and pKa of oral drugs are formulated to optimally release active ingredients in the stomach for acidic drugs and in the intestine for basic drugs. The drug must reach a specific tissue receptor site to elicit the desired effect. Since the per os route of administration is recognized as the method of choice and is used most extensively in therapeutics, it is important to recognize deviations in gastrointestinal absorption. Similarly, a dysfunction of the circulatory system, in transporting the active ingredient to its locus of action in a concentration sufficient to exert the drug effect, would prevent proper drug distribution.

Since most drugs are not absorbed in the stomach, radiation-induced gastric retention and/or decreased motility delays emptying and therefore retards absorption. In addition, it is not feasible to give oral doses to the vomiting or moribund radiation casualty. For these reasons parenteral therapy is necessary.

Detrick et al. (75) investigated the influence of 525 R whole-body X-irradiation on the intestinal absorption and elimination of N'-methylnicotinamide in rats. A significant increase in elimination of this metabolite via the intestinal tract was found after irradiation, and the increase was maintained even when histological evidence of tissue repair was observed. The highest elimination rate was seen on days 3 and 5. The authors attributed the radiation-induced increase in excretion of N'-methylnicotinamide to an increase in the transmethylation process. Other studies have shown that radiation injury to the intestine results in a profound decrease in the absorption and/or transport of essential metabolites, particularly on the third day (59, 60, 61). An electron microscopic examination of the 525 R whole-body irradiated intestine revealed acute, mild focal areas of mitochondrial swelling, swollen double-walled organelles containing a dense homogeneous matrix, and fine cytoplasmic vacuolization present in comparatively unaffected crypt and villar epithelial cells over a 17-day period (76).

Anesthetic agents may be required in the radiation exposed patient requiring surgery. Administration of anesthetics (cyclopropane, ethylene, nitrous oxide, ether, and thiopental sodium) caused no detrimental effect, neither increasing the 30-day mortality nor decreasing the survival time of X-irradiated rats (77). Ethylene exhibited beneficial effects by significantly increasing median survival time whereas rats showed a decreased tolerance toward mid-lethal doses of cyclopropane when anesthesized seven days after X-ray exposure. Following chloroform anesthesia, recovery of irradiated rats was slower than controls and muscular spasms were observed. The hepatotoxicity of chloroform may account for the gross differences in survival time. Burdick (78) previously found significant changes in the number of thirty-day survivors (rats) when thiopental sodium was given seven days after X-ray exposure. Barbital, hexobarbital, and pentobarbital plasma half-times were determined (79) in male monkeys before and after 1,500-, 5,000-, and 10,000 rad whole-body doses of mixed gamma-neutron radiations. Of the three drugs, the duration of action of barbital was altered the

most. Because barbital depends upon renal excretion, while hexobarbital and pentobarbital are detoxified by liver enzymes, the results indicated that irradiation affects the former system more than the latter.

The influence of mixed gamma-neutron radiation has been studied on the acute toxicity of 4 classes of drugs (73). The drug dose-response curve (LD_1 to LD_{90}) was determined after radiation exposures that caused the death of mice from hematopoietic failure, gastrointestinal injury, or central nervous system effects within 6 days. As expected, the LD_{50} values for most drugs were altered significantly in irradiated mice and drugs were more toxic by day 6 following irradiation. Toxicity was related to radiation dose and post-irradiation time; however, not all drugs proved to be more toxic to irradiated than control mice. For example, anticonvulsants (diphenylhydantoin, phenobarbital, and mephenytoin) were more toxic to mice receiving 1,000 and 10,000 rad doses, while psychopharmacologic agents (chlorpromazine, triflupromazine, and chlordiazepoxide) were less toxic to mice receiving 1,000 rad doses but more toxic to those receiving 10,000 rad doses. Alterations in drug metabolism induced by radiation might explain the results obtained. Nair et al. (80) have shown that the potency, onset, and duration of anticonvulsant action of acetazolamide was enhanced in head X-irradiated rats; an effect that may be related to increased entry of the drug into specific brain regions. Enhancement of barbiturate hypnosis was found in cephalic X-irradiated rats, the effect depending on the radiation dose and post-irradiation time (81). Prolonged thiopental hypnosis was found after high (5,000 and 10,000 R) doses of radiation. Interestingly, no inhibition of phenobarbital microsomal enzyme induction was produced by radiation (81).

Doull (82) reported irradiated animals exhibit few qualitative or quantitative changes in their response to therapeutic or toxic doses of the commonly used central nervous system stimulants and depressants, anesthetics, analgesics, muscle relaxants, antihistaminics, cardiac drugs, antithyroid agents, diuretics, cholinergic agents, and many autonomic drugs. Frik et al. (83) made a comparative toxicologic study of 64 drugs by determining the LD_{50} in nonirradiated mice and in mice receiving 500 R whole-body irradiation 4 days prior to drug administration. Sixteen drugs showed an increased toxicity and 14 drugs showed a decreased toxicity in irradiated animals; the remaining substances were equally toxic in both groups. The preparations examined, listed according to pharmacologic groupings,

and the summarized results are shown in Table 1. Drugs showing an increased toxicity generally have a paralyzing or exciting effect upon the central nervous system, while drugs exhibiting decreased toxicity affect the circulatory system. The authors found the majority of drugs used in human radiation treatment were not more toxic to irradiated mice under the conditions of the test.

Several radiation-induced changes have been postulated to explain the altered effectiveness of drugs in irradiated rodents. These include: altered permeability of the blood-brain barrier, alteration of liver detoxifying enzymes, and sensitization of the brain to drugs. The list should be expanded to include more therapeutic agents necessary for the treatment of radiation injured individuals or combinations of radiation and traumatic injuries of the type anticipated in military operations.

Attempts to elucidate a model system to mimic gastrointestinal radiation damage have been made to test probable therapeutic drug regimens. Villus epithelial cells of mice that had received daily injections of nitrogen mustard (inhibition of cell proliferation in G_2 as does X-irradiation) for 4 days showed a progressive loss of ribosomes, reduction in terminal web material, and failure to absorb and transport lipid in normal amounts from the gut lumen to the lamina propria (84). A progressive shortening of crypts and villi and occasional loss of epithelium was also observed by day 4. Hampton (84) intimates these results parallel to a large extent conditions existing in the intestinal epithelium in mice 3 to 4 days post treatment with 3,000 rad of X-rays. The author (85) previously attempted to produce epithelial loss by holding the crypt epithelium in sustained arrest for 4 to 5 days by daily injections of colchicine, a drug that arrests mitosis in metaphase. Not only did the experiments fail to produce denudation, but the cytological changes descriptive of radiation damage and extreme shortening of crypts and villi failed to develop, even though the proliferative compartments of many crypts were destroyed. The radiomimetic damage and altered effects should be correlated in irradiated animals and eventually in man. Drug profile examinations in normal, nitrogen mustard treated, and irradiated animals should be attempted to validate the possible use of this system.

The absorption, distribution, and extretion of the common drugs therapeutically indicated for radiation-induced injuries should

TABLE 1

Gruppe	Wissenschaftliche Kurzbezeichnung	Warenname	LD 50 mg/kg Kontroll-tiere	Mit 500 R bestrahlte Tiere	Signifikante Differenz (unbestrahlt = 100%)
1	Clemizol-Penicillin-G	Megacillin	150 000 IE*	150 000 IE*	
	Streptomycin	Streptomycin „Bayer"	525	735	+ 40%
	Chloramphenicol	Leukomycin	2350	1920	
	Erythromycin	Erycin	378	435	
	Kanamycin	Kanamytrex	1170	975	
	Tetracyclin	Tetracyclin „Bayer"	184	184	
	Sulfamonomethoxin	Durenat	865	990	
	Isoniazid	Rimifon	251	167	− 34%
2	Äthylalkohol	–	528	607	+ 14%
	Hexobarbital	Evipan	317	317	
	Phenobarbital	Luminal	382	246	− 25%
	Methitural	Thiogenal	454	222	− 51%
	Methyprylon	Noludar	530	530	
3	Promethazin	Atosil	172,5	120	− 30%
	Chlorpromazin	Megaphen	187	154	− 18%
	Reserpin	Sedaraupin	7,5	5,0	− 23%
	Prothipendyl	Dominal	135	135	
	Diazepam	Valium	37	43,5	
	Chlordiazepoxyd	Librium	175	203	+ 16%
4	Morphium hydrochloricum	–	432	432	
	Pethidin	Dolantin	135	122	
	Natr. salicylic.	–	500	562	
	Cinchophen	Atophan	512	463	
	Aminophenazon	Pyramidon	524	375	− 29%
	Phenylbutazon	Butazolidin	285	248	− 13%
5	Pentetrazol	Cardiazol	87	85	
	Bemegride	Eukraton	29,5	29,5	
	Lobelin	Lobelin „Ingelheim"	43,5	40,5	
	Coffein. natr. salicyl.	–	224	232	
6	k-Strophanthin	Strophantin „Boehringer"	2,4	3,1	+ 29%
	Protoveratrin	Ebrantan	4,1	5,0	+ 22%
	Aminophyllin	Euphyllin	37	30,8	− 17%
	Dioxypropyl-theophyllin	Theal	195	124	− 26%
	Dipyridamol	Persantin	243	286	+ 18%
	Prenylamin	Segontin	59	39	− 34%
	Jproveratril	Isoptin	56	59	

* Angabe hier nicht in mg, sondern in Internationalen Einheiten.

Table 1 (continued)

Gruppe	Wissenschaftliche Kurzbezeichnung	Warenname	LD 50 mg/kg Kontrolltiere	Mit 500 R bestrahlte Tiere	Signifikante Differenz (unbestrahlt = 100%)
7	Adrenalin	Suprarenin	8,4	10,5	
	Noradrenalin	nor-Epirenan	19,5	16	
	Synephrin	Sympatol	730	840	
	Pholedrin	Veritol	156	212	+ 36%
	Aethyladrianol	Effortil	245	400	+ 63%
	Hydroxyphenylaethanolamin	Novadral	85	195	+ 130%
	Ephedrin. hydrochl.	–	220	270	+ 23%
	Isoprenalin	Aludrin	565	530	
	Orciprenalin	Alupent	370	440	
	Bamethan	Vasculat	185	185	
	Methamphetamin	Pervitin	8,1	6,2	– 15%
	Prolintan	Katovit	18,2	19,2	
8	Azapetin	Ilidar	173	134	– 23%
	Tolazolin	Priscol	78	111	+ 42%
	Thymoxyalcylamin	Opilon	112,5	125	+ 11%
	Nethalide	Alderlin	102	92	– 10%
9	Acetylcholin-chlorid	–	188	164	
	Neostigmin	Prostigmin	0,3	0,5	+ 66%
	Carbachol	Doryl	3,3	2,8	
10	Atropin-chlorid	–	180	195	
	Butylscopolamin	Buscopan	156	112	– 28%
	Orphenadrin	Mephenamin	78	64,5	– 17%
11	Pheniprazin	Catroniazid	71	93	
	Phenelzin	Nardil	139	124	
12	d-Tubocurarinchlorid	Curarin HAF	0,3	0,38	+ 27%
	Gallamin	Flaxedil	15,4	16,3	
	Procain	Novocain	160	160	
	1-Benzyl-3-äthyl-6,7-dimethoxy-isochinolinhydrochlorid	Eupaverin	385	405	

(Courtesy W. Frik; Ref. 83).

be explored more fully. Drugs are generally converted to less toxic, more water soluble metabolites and excreted. In the irradiated individual, if the inherent detoxication ability is not intact, each additional dose may allow an increase to a toxic level. The liver represents the major organ of metabolism and, if functionally impaired by radiation, may permit drug recycling with eventual toxic manifestations. More pharmacologic post-irradiation studies should be conducted for frequently prescribed medications.

(See Section VII, Suggested Areas for Future Research, p 66)

VII. SUGGESTED AREAS FOR FUTURE RESEARCH

IMMEDIATE POST-IRRADIATION CELLULAR EVENTS

Research should continue on the sequence of cellular events that occur in the gastrointestinal tract of man following radiation exposure. Techniques for *in vivo* evaluation of crypt cell regeneration and proliferation warrant further refinement. Recent advances in tissue culture techniques afford a new approach to study intestinal cell responses to radiation. (See Section VI B, p 26).

MORPHOLOGIC RESPONSES

Changes in histology and cellular proliferation kinetics observed in man resemble those in animals following sublethal irradiation. Therefore, research should continue in animals to establish the critical aspects of cell renewal patterns in the recovery process.

The emphasis in most animal investigations has been on the intestinal epithelium. Much less is known about changes in the mesenchymal elements of the gastrointestinal system such as vascular, muscle, and connective tissues. Radiation-induced changes in the submucosa and muscle coats of the intestine are incompletely understood and should be investigated.

The rat exteriorized-intestine model is useful in the study of the cellular repair process following radiation exposure. Additional studies with this technique should assist in understanding the characteristic changes observed in whole-body irradiated animals and the discontinuous cellular changes found in the exteriorized irradiated intestine. (See Section VI C, p 28).

GASTROINTESTINAL AND HEMATOPOIETIC CORRELATIONS

Renewal of the functioning cells of the intestine is possible if the integrity of the epithelium and lamina propria is maintained. Research should emphasize the prevention of injury to these components of the intestinal mucosa and the crypt cell proliferation after basement membrane destruction by ionizing radiation. Restorative capacity and mechanisms of regeneration in the hematopoietic and gastrointestinal systems should be investigated further. (See Section VI D, p 37).

INTESTINAL MOTILITY AND MALABSORPTION

Additional research is necessary on the absorption, distribution, metabolism, and excretion of essential elements, water, and drugs after radiation exposure. Extension of animal studies to primates would provide information useful in the treatment of human subjects. Radiation-induced changes in the metabolism of nutrients and drugs could be carried out in patients exposed to radiation. In addition, the effects of radiation on the autonomic nervous system in the control of intestinal motility should be investigated. (See Section VI E, p 40).

INTESTINAL FLORA CHANGES

Even though intensively studied, the mechanisms responsible for systemic infections following irradiation are not fully understood. Invasion and infection of the intestinal tissues by opportunistic pathogens may be related to increased permeability of the intestinal wall. Further investigation on factors affecting microbial pathogenicity in the irradiated intestine, the biochemistry of cell wall integrity, and the role of intestinal motility are required. The ecology and pathogenicity of the resident flora in the irradiated gastrointestinal tract require further study. (See Section VI F, p 43).

ANTIBIOTICS IN RADIATION THERAPY

Controlled studies should be made on patients receiving enteric radiation therapy to evaluate the virtues of antibiotic therapy in preventing tissue invasion by opportunistic microorganisms. Microscopic examination of biopsy material from the small bowel, colon, and rectum of patients would assist in determining the causes of the histologic changes and their relation to the altered flora, the radiation dosage administered, and antibiotic therapy. (See Section VI G, p 45).

RADIATION-INDUCED VOMITING

The cause of vomiting induced by radiation of isolated parts or major portions of the gastrointestinal tract requires elucidation. Future research should include careful documentation of the time of onset and severity of nausea and vomiting in man as related to the dose of whole-body irradiation. Animal studies of radiation-induced vomiting can assist in developing better treatment regimens for radiation injury in man. (See Section VI H, p 47).

TRANSPORT OF FLUID, ELECTROLYTES, NUTRIENTS AND OTHER ESSENTIAL ELEMENTS

The biochemical events associated with alterations in fluid, electrolyte, and nutrient balance following radiation exposure should be analyzed critically. Additional investigations are necessary to clarify the basic mechanisms that underlie transport of fluid and electrolytes in the diarrhea and dehydration associated with post-irradiation injury. For example, serial physiological and biochemical determinations could be carried out in patients exposed to radiation. Studies of this type may suggest improved treatment regimens. Research on the role of bile in diarrhea and its relationship to changes in intestinal electrolyte transport following radiation injury should be continued. (See Section VI I, p 50).

ALTERATIONS IN DRUG METABOLISM

Drug action and toxicity may be altered in the irradiated individual. Studies of therapeutic agents used in the post-irradiation treatment of combined radiation and traumatic injuries anticipated in the soldier should be expanded. Of particular importance are the pharmacodynamic and metabolic aspects of these drugs in the post-irradiation state. (See Section VI J, p 55).

VIII. APPENDIX

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Cell Renewal Patterns.
New Engl. J. Med. 279: 248-258 (1968).

"In their preparation for division, cells progress through several discrete metabolic intervals during which their many components are replicated, so that they may be donated to the progeny cells. The total time occupied by the events involved in the formation of two daughter cells from one parent cell is referred to as the generation or replication time. Two major intervals thereof are DNA synthesis, when the amount of this material is doubled, and mitosis, when the chromosomes are rearranged prior to the division of the cell. These two intervals are each separated by periods G_1 (gap_1) between mitosis and DNA synthesis and G_2 (gap_2) between DNA synthesis and mitosis, during which other metabolic events are in progress.

"With the initiation of DNA synthesis, component nucleotides are mobilized from intracellular pools and are polymerized. Since this occurs only during a particular part of the replication cycle, the introduction into the pool of the radioactive DNA precursor, ^{3}HTDR, will label all cells that are synthesizing DNA. The exposure to a single administration of ^{3}HTDR, *in vivo*, will be for one relatively brief interval, usually less than an hour, depending upon the route of administration. Thereafter, the incorporated radioactive material is "fixed," and all labeled cells may be considered as derived from this initially exposed population or cohort of cells. The sectioned tissue (2 to 5 μ in thickness) is layered with photographic emulsion, stored in darkness for an appropriate time and developed. The location of the radioactive material is revealed by the presence of tiny black dots, caused by the reduction of the silver in the emulsion in the track of the beta particle from tritium. The developed autoradiograph may be lightly stained through the emulsion to assist in the histologic identification of labeled and unlabeled cells in the interphase and mitotic stages of the generation cycle. Hence, with the passage of time, as the labeled cells complete DNA synthesis, they

will appear as labeled mitoses. By scoring of the changing percentages of labeled mitoses, at appropriate times after the administration of ^{3}HTDR, the movement of the initially labeled cohort and its progeny cells may be followed through successive waves of replication. From the curves derived from these data, the several parts of each generation cycle may be calculated (i, ii). The generation time is measured as the interval from the initiation of labeling in one cycle to that of the succeeding cycle. DNA synthesis is the time between the 50 per cent intercepts of the ascending and descending limbs of the mitotic labeling curve. G_2 plus mitosis may be estimated as the time required for 50 per cent of the mitoses to have become labeled in the first cycle. By subtraction of the times occupied by DNA synthesis and G_2 plus mitosis from the generation time, the G_1 interval is derived. Rough estimates of the amount of radioactive material may be made if the grains over labeled nuclei are counted. Their numbers will be lowered by approximately half with each successive replication cycle, by dilution with newly synthesized nonradioactive DNA. The amounts of radioactive material administered are expressed in microcuries (μc), and the specific activity of the preparations in curies per millimole of thymidine (c/mM). The dose of ^{3}HTDR has usually been based upon the animal weight, hence it is expressed as microcuries per gram (μc/gm)."

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Cell Population Kinetics in Intestinal Epithelium of Mouse.
Exp. Cell Res. 17: 420-438 (1959).

(87) Conard, R. A.
Some Effects of Ionizing Radiation on the Physiology of the Gastrointestinal Tract: A Review.
Rad. Res. 5: 167-188 (1956).

"There are several possible mechanisms involved in the radiation-induced gastrointestinal symptomatology and malfunction. Let us first consider the anorexia, nausea, and vomiting which occur early after irradiation. How much of this symptomatology is produced by direct effect on the gastrointestinal tract, and how much is an indirect effect? We know that in radiation therapy such symptomatology may be produced by irradiation of parts of the body not involving the gastrointestinal tract. In the rat, Swift et al. (i) have shown that the emptying defect of the stomach may be induced by radiation of parts other than the gastrointestinal tract, particularly the head. Bowers et al. (ii) have shown that extirpation of the gastrointestinal tract from cardia to rectum did not prevent the emetic response to irradiation (as determined by gag reflex, etc.). Therefore, it seems necessary to assume that there is an indirect mechanism, possibly producing reflex vomiting through action on the higher nerve centers. Reflex vomiting of this nature is believed to be induced by lowering the threshold of these centers so that stimuli usually incapable of invoking vomiting may then do so. Recent experiments in dogs by Chinn and Wang (iii) indicate that the emetic chemoreceptor trigger zones are essential for the emetic effect of irradiation rather than the vomiting center itself. The emetic effect of irradiation is not a direct one on the trigger zones, since shielding of these zones does not eliminate vomiting (iv, v). It has been demonstrated that in the cat, however, neither ablation of the medullary emetic chemoreceptor trigger zone, frontal decortication, nor decerebration abolished the emetic response (ii). It seems necessary to assume that some sort of toxic substance or substances result from irradiation which are capable of inducing emetic action via the central nervous system. Since it is well known that when a portion of the gastrointestinal tract is included in the field of radiation therapy the resulting sickness will be more severe, there must be some direct effect of radiation on the gastrointestinal tract which aggravates the symptomatology. There are several radiation-induced changes in this system which may play an etiological part. In the first place there are large amounts of

radiosensitive tissue in this organ system showing injury very soon after irradiation which might afford a good source of the "emetic" substance. Of importance also may be an increased bombardment of the higher centers with efferent impulses from an injured organ, injury which is borne out by profound histopathological evidence of damage and functional derangement."

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XI. GLOSSARY

Crypt	The crypts of Lieberkühn or intestinal glands are tiny pockets lying between the villi. Their blind ends dip deeply into the mucous membrane, reaching as far as the muscularis mucosae. They are lined by epithelial cells continuous with those covering the summits of the villi.
Enterochromaffin cells . .	Among the columnar cells are specialized cells, also called argentaffine cells, that stain with silver or chromium salts. These cells are of particular interest because they secrete serotonin, or at least synthesize its precursor, 5-hydroxytryptophane.
Goblet cells	Converted epithelial columnar cells lining the intestinal glands that secrete mucus.
Lamina Propria	The layer of connective tissue underlying the epithelium of the intestinal mucosa.
Mitosis	The process of division of somatic cells that results in the formation of two daughter cells with exactly the same chromosome number and DNA content as the original cell.
Rad	(Acronym for radiation absorbed dose.) The basic unit of absorbed dose of ionizing radiation. A dose of one rad means the absorption of 100 ergs of radiation energy per gram of absorbing material.

Roentgen (R)	A unit of exposure to ionizing radiation. It is that amount of gamma or X-rays required to produce ions carrying 1 electrostatic unit of electrical charge (either positive or negative) in 1 cubic centimeter of dry air under standard conditions.
Terminal Web	Fibrillar cytoplasm, beneath the microvilli of intestinal absorbing cells, which is free of cytoplasmic organelles.
Villus	The villi intestinales are numerous minute filiform projections from the mucous membrane of the small intestine which give to its surface a soft velvety appearance; they contain blood vessels and lacteals. The epithelium covering the villi is the same type as that lining the crypts, and consists of a single layer of columnar cells with certain specialized cells interspersed among them. The free end of each columnar cell, next to the lumen of the intestine, is provided with a specialized cuticular border, resembling the brush border of certain renal tubular cells. The brush border of the surface epithelial cells of the villi is composed of microvilli approximately 1μ in length and 0.1μ in width.

PART II

THE GASTROINTESTINAL SYNDROME IN ACUTE RADIATION INJURY

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I. INTRODUCTION

This review of radiation effects in the digestive system is concerned primarily with changes in the irradiated human, especially those conditions likely to occur under conditions of nuclear warfare.

The post-irradiation clinical picture characterized by rapid onset of nausea and vomiting, followed shortly by severe diarrhea and fever and, if untreated, death within a few days, is produced by radiation doses exceeding those required to produce the "hematopoietic syndrome" but smaller than those causing death from central nervous system damage. The complex of signs and symptoms is referred to variously, as "intestinal mode" of acute radiation injury or death, "acute intestinal radiation death," "the gastrointestinal (G.I.) syndrome," and, in the earlier literature, as "radiation sickness." The latter term has been applied especially to patients receiving radiation therapy. It includes a considerably wider range of radiation-induced gastrointestinal derangements than the other terms listed, and hence is somewhat ambiguous.

A number of reviews of the gastrointestinal (G.I.) syndrome have been published and these have been consulted extensively in the preparation of the present report. Relevant references cited in the text of this report are annotated in the bibliography. In addition, the bibliography lists separately, and without annotation, a group of review articles and books selected as being authoritative and, as a group, representative of the literature; and a group of papers that, although not cited specifically in the text, would provide additional highly pertinent documentation. Where feasible, references describing observations of human subjects and representing the more recent literature have been selected.

II. CHARACTERISTICS OF THE GASTROINTESTINAL SYNDROME

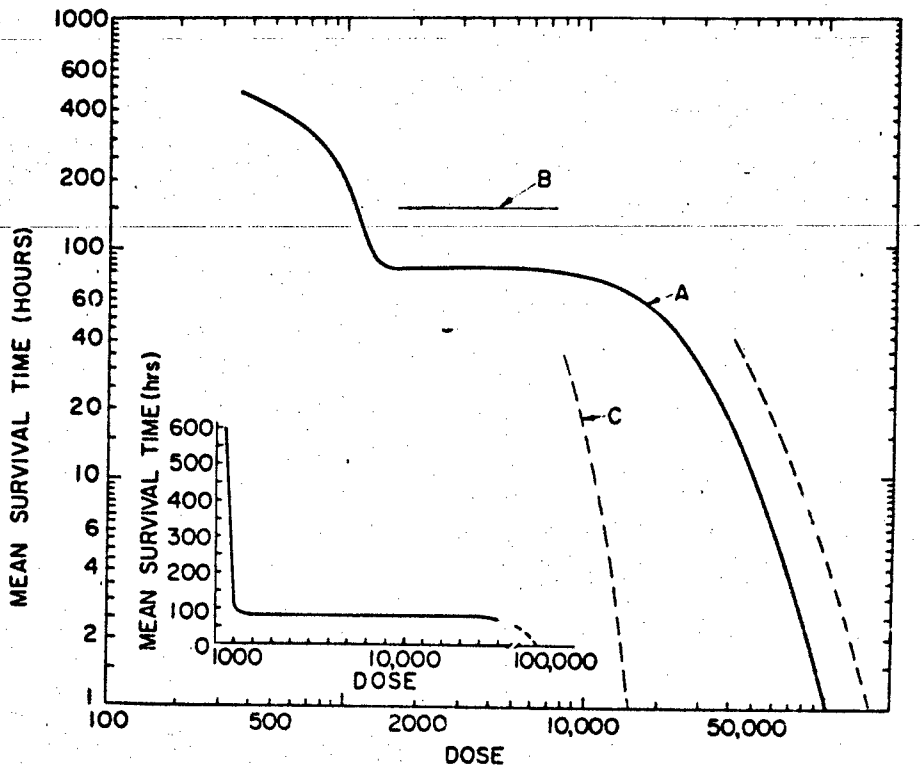
Quastler formulated a particularly succinct description of the G.I. syndrome in his classical paper on the subject, listing its characteristics as follows: "It occurs with doses of about 1 to 10 KR; the survival time is about 3 to 5 days and is nearly invariant with dose; the target organ is the small bowel; and there is a distinctive pathology, namely loss of epithelial lining of the intestine" (1).

Death will occur usually within a week following onset of the G.I. syndrome if supportive therapy is not available. There is evidence, however, that some lives may be saved by intensive therapy that would replace fluid and electrolyte loss, combat infection, and replace or compensate for total destruction of hematopoietic tissue. Depending upon the severity of the illness, the facilities and medical expertise available and on the number of casualties to be coped with, the triage officer might classify these patients as either "survival possible" or "survival virtually impossible."

Referring to the G.I. syndrome as a "mode" of death has merit in that this syndrome represents a clinical picture that differs from the "bone marrow" or "hematopoietic" syndrome with respect to the kind and severity of signs and symptoms, their time of onset, rate of progression to a fatal outcome, and the probability of such an outcome. A recent monograph by Bond, Fliedner and Archambeau describes the syndrome particularly well, placing it in the context of acute radiation injury generally (2). Figure 1, reproduced from this monograph, demonstrates the characteristic three-component curve observed when mean survival time is plotted as a function of dose for most species that have been studied, including man. Although radiation dose has little influence on survival time following exposure to radiation doses sufficiently large to result in the G.I. syndrome, both dose rate (3, 4, 5, 6) and type of radiation (7, 8) have a marked effect on the effectiveness of a given total dose.

In man, the G.I. syndrome is manifest soon after exposure by nausea, vomiting, and anorexia; the patient is acutely ill, lethargic, and weak (9, 10, 11, 12, 13). Diarrhea begins during the first day after exposure and as the syndrome develops, blood is characteristically present in the liquid stools. The small intestine becomes denuded of its epithelial covering, villi are flattened, and the mechanisms for absorbing and retaining fluids,

Figure 1



(Fig. 5.1 in Ref. 2) Mean survival times as a function of dose following whole-body exposure of the mammal to ionizing radiation. Initial component is dose-dependent and represents lethality associated with the bone marrow syndrome; second component (~1000 to 10,000 R) represents lethality associated with the gastrointestinal syndrome. Note that mean survival time is constant (3.5 days) over entire dose range spanned by this part of the curve (B). The last dose-dependent portion of the curve represents lethality associated with central nervous system injury. Curve C indicates approximate limits for different species.

electrolytes, and nutrients are disrupted. Bacteria have access to the blood and lymphatic circulation, a difficulty that is compounded by the nearly absolute neutropenia that develops within a few days, by destruction of the intestinal lymphoid tissue, and by the rapidly falling platelet count. As one might expect, early onset of fever is characteristic of the G.I. syndrome.

Although the term, "G.I. syndrome," correctly suggests that the critical organ is the gastrointestinal system, it is important to remember that in the classical form observed following whole-body exposure, it represents a greater degree of injury to all tissues than does the hematopoietic syndrome. The extensive injury in other tissues, especially of proliferating cell lines in other tissues, contribute significantly to the development of the clinical picture and to lethality.

Considerable controversy exists concerning the relative significance of the component derangements such as denudation of intestinal epithelium, overwhelming infection, and fluid and electrolyte loss as determinants of the lethal effectiveness of radiation doses that produce the G.I. syndrome (2, 14). Another potentially important cause of acute intestinal radiation death, septic shock, is emphasized in a later section of this review. If the G.I. syndrome carried with it a completely hopeless, instead of a very poor prognosis, the controversy would be merely academic. Since appropriate therapy may be expected to save the lives of some patients developing the syndrome, however, the issue assumes considerable practical importance.

III. KINETICS OF CELLULAR PROLIFERATION

In all mammalian species studied, the radiation-induced G.I. syndrome is characterized by immediate interruption of proliferation by the cells in the crypts of the small intestine. Normally the intestinal epithelium represents a steady state system. New cells produced by mitosis of cells in an area of the crypt referred to as the "crypt cell column," or "proliferating compartment" move upward along the villus as new cells come off the epithelial production line behind them (1, 2, 15, 16). Each villus thus supports cells of all ages that are produced by a group of crypts at its base Although the mechanism and exact route of cell migration are not known, there is good evidence that the cells at the tips of the villus are at or near the end of their life spans and eventually are sloughed into the intestinal lumen. This orderly progress suggests that the cells are, in a sense, pushed along the villus. In studies comparing irradiated germ-free and conventional mice, however, although the radiation blocked mitosis of crypt cells in both groups of mice, newly produced crypt cells of germ-free mice took twice as long to migrate from crypt to the tip of the villus as did their counterparts in conventional mice (17, 18). It also took twice as long for villi of germ-free mice to become denuded of epithelium. This might suggest that the cells tend to be "pulled" at a rate determined by cell loss at the tip (19).

It is possible to remove individual crypts from the intestine. This procedure, used in conjunction with radioactively labeled DNA precursors (tritiated thymidine) has made possible the measurement of cellular proliferation rates and the duration of various stages of the cell cycle in normal and irradiated animals (2, 7, 8, 15, 16, 19, 20). As indicated by data in Tables 1 and 2, similar measurements of cell proliferation kinetics in the epithelium of the normal human gastrointestinal tract have also been made (21).

The changes in cellular proliferation in the epithelium of the small intestine of the mouse following X-irradiation are highly reproducible. This experimental model of a rapidly proliferating cell system has, in fact, been extensively employed by those concerned with cellular effects of irradiation as well as by those interested in the effects of irradiation on the gastrointestinal system (2, 7, 8, 19, 20, 22).

Intestinal epithelial cell proliferation may, of course, be influenced by agents other than ionizing radiation (17, 18, 23, 24).

Table 1

CELL PROLIFERATION IN THE ILEUM

	Mouse	Man
Crypt cell generation time	11 hr	24 hr
Villus transit time	26 hr	80 hr
Total cell system transit time	2 days	1 week
Death from G.I. syndrome	3.5 days	1 week

Table 2

CELLULAR PROLIFERATION IN G.I. EPITHELIUM OF MAN[1]

	Region of Gastrointestinal Tract			
Variable	Stomach[2]	Ileum	Colon	Rectum
Cells in crypt column[3]	58	32.6	92	64
Cells in S[4]	6.8	2.9	16	10
Fraction labeled, prolifer. compart.[3]	0.3	0.09	0.17	0.16
S period	10 hr	11 hr	14 hr	10 hr
Proliferation rate[5]	0.3	0.8	1.2	2.5
Mean generation time	~1 day	>15 hr (~24 hr)	>16 hr	>13 hr

1 From data presented in Ref. 21, based on serial counts of labeled mitoses following injection of ^{3}H thymidine.
2 Proliferating region is on neck of gastric gland; entire gland is not included in sections.
3 Proliferating compartment; single crypt.
4 DNA synthesis: 30-60 min after injection of $^{3}HTdR$ and before first cell division.
5 Cells produced/100 cells/hr.

In the mouse system that has been widely studied, it is usually assumed that inclusion of appropriate controls provides adequate assurance that extraneous influences would be recognized as such. No such assurance is possible in the case of irradiated patients who, being humans and exhibiting considerable individual variability, are not on a standard dietary regimen, and in fact, are not "standardized" in any sense. Furthermore, when the gastrointestinal syndrome develops in man, therapeutic management will be required, and physicians responsible for medical care of such patients must be mindful of more than interrupted proliferation of intestinal epithelium even though this be the fundamental derangement.

Intestinal epithelium, like hematopoietic tissue, has a remarkable capacity for recovery, and this can also be evaluated by studying the kinetics of cellular proliferation after the intestine has been severely damaged by radiation (2, 7, 8, 15, 19, 20, 24, 25, 26, 27, 28). Two compensatory or recovery mechanisms have been demonstrated in investigations using irradiated experimental animals: (a) acceleration of the cell generation cycle, and (b) an increase in the number of cells in the proliferative compartment (1, 7, 8, 15, 16, 19, 20) The intestinal crypt cells also appear to have a great capacity for true repair of intracellular lesions when studied in vitro (29).

Lesher has shown in mice, following exposure to 1000 R of X-rays, that the entire population of crypt cells (including those usually considered to be undergoing maturation in a zone at the neck of the crypt) can be recruited into the proliferating compartment. This approximately eightfold increase in the size of the proliferating pool is enhanced by shortening of the cell generation cycle (15). Cell production was blocked for 4½ hours after 300 R, remained depressed for 10 hours, and during the ensuing rapid recovery, cell production reached a maximum rate that was approximately ten times normal. Cell production rates after higher radiation doses were accelerated even more.

Mechanisms for controlling the size of the proliferating pool and the length of the cell cycle have yet to be identified, but there is increasing evidence, from studies utilizing parabiotic rats, that a humoral agent may be one of the important normal control mechanisms (30). If one parabiont has a small segment of ileum removed surgically, both partners subsequently show a remarkable and equal increase in the number of proliferating intestinal crypt cells in all segments of the intestine. This effect appears to be independent of shortening of the mitotic cycle (29).

IV. INTESTINAL ARCHITECTURE

The grossly altered architecture of the heavily irradiated gastrointestinal tissue cannot be attributed solely to cessation of crypt cell proliferation, although that event may underlie some of the other changes. Many alterations are the same as those seen in the intestine that is injured by agents other than irradiation (24, 31). Flattening of the villi, for example, and absence of typical epithelial covering are also observed in cholera and salmonellosis (31). It is interesting that the flattened villi are not truly denuded of epithelium, but are covered, at least until the terminal phase of the syndrome, with a layer of cells that spread out to form an extremely thin sheet. This covering may be dislodged particularly easily in the irradiated intestine and is probably torn off rather frequently during laboratory processing of histological sections. It may also be dislodged relatively easily from the tissue in situ. The bond between the epithelium and its base appears to be less easily broken in irradiated germ-free animals than in irradiated conventional animals (16, 18). The phrase, denuded of epithelium, is used throughout this review with the understanding that denudation is not necessarily complete.

It is tempting to speculate that normal migration and spreading of epithelial cells along the villi represents a relatively specialized type of relationship of epithelium to its basement membrane and its underlying supportive tissue, a relationship in which the epithelium maintains a high degree of intrinsic control over cell movement, form, and position. This notion is compatible with the observation of initially "squamoid" and subsequently cubiodal metaplasia of epithelial cells that cover the villi during early recovery from radiation-induced injury and also in conditions such as cholera (31). As Patt has pointed out, there is little information available about the number of mature cells that are necessary to support life (19).

During preparation of this review, no published reports were found describing experiments designed to investigate migration patterns of normal intestinal epithelium or to measure its capacity to spread in response to loss of large numbers of epithelial cells. If mucosal cells were found to have a high degree of autonomy, this might conceivably be exploitable through development of methods for accelerating movement of remaining viable cells. It might not be unduly fanciful even to consider the possibility of transplantation of cell suspensions onto the injured surface.

Vascular changes are prominent in the small intestine of rats developing the G.I. syndrome. Occlusive lesions can be demonstrated in many vessels throughout the intestine, particularly in the smaller arterioles. Soon after exposure these changes consist primarily of spotty arteriolar narrowing, but at the time that death occurs as a result of the G.I. syndrome, filling of mucosal and submucosal vessels by perfusion medium is sharply decreased, and there is no filling at all in some areas. Numerous hemorrhagic lesions may be observed in the mucosa at this stage (2, 31).

V. INTESTINAL MOTILITY

The large doses of radiation required to elicit the G.I. syndrome have profound effects on gastrointestinal motility. In the monkey, which seems to respond to such doses much as man does, vomiting occurs shortly after exposure. After subsiding temporarily, it recurs and is accompanied by anorexia and severe diarrhea (33). This pattern is strikingly similar to that observed in those Japanese atomic bomb victims who later developed the G.I. syndrome (2, 7, 12, 13).

Radiation affects motility of the gastrointestinal tract through diverse mechanisms, but these do not include direct effects on the muscularis. Conard demonstrated that in several species of experimental animals, altered intestinal tonus and increased contractions could be observed as early as one minute after exposure. Similar effects could be elicited by irradiating isolated intestinal loops. The effects were inhibited by anticholinergic agents and potentiated by physostigmine and acetylcholine (34). Bacterial endotoxins have been shown to influence motility through their effect on the central nervous system (35), and radiation effects on ganglia of the autonomic nervous system in the intestine have been described (34, 36). The extensive Russian literature emphasizes the role of both the central nervous system and the autonomic nervous system in altering gastric and intestinal motility in the irradiated animal (37).

Motility is one of the most important influences on the distribution and number of bacteria in various parts of the normal intestine. It accounts for the remarkable paucity of organisms in the upper portion of the normal small bowel (38). The number and distribution of bacteria in the intestine can be altered experimentally by means of medications that influence motility (38, 39). The high intestinal coliform counts in rats with bile diverted from the intestine have been attributed to decreased intestinal motility.

VI. ROLE OF BILE

It has been suggested in previous sections of this review that bile may affect the histology of the intestinal mucosa in several ways. The detergent-like action of bile salts tends to deplete the goblet cells of mucus and in the absence of bile, goblet cells are greatly increased in number (39). They are seen in relatively greater numbers even in the heavily irradiated animal that has had bile diverted from the intestinal tract.

Absorption of bile salts through the epithelium is markedly decreased within three days after irradiation. The output of bile, however, tends to increase at the same time, the result being that a considerable amount of bile reaches the colon. Resorption of water by the right colon is decreased by the presence of bile salts, which exert an osmotic effect, enhancing diarrhea. If bile is diverted from the intestine, diarrhea can be controlled in rats irradiated over the intestines only (40, 41, 42, 43). Although bile appears to contribute significantly to the development of the G.I. syndrome, the presence or absence of bile appears not to influence cell proliferation kinetics (43).

VII. ABSORPTION AND RESORPTION

There is molecular traffic in both directions across the mucosa of the normal intestinal epithelium. The small intestine, which is highly vulnerable to radiation injury, is also the principal site for absorption of nutrients. Although the villi are not invariably truly denuded in the G.I. syndrome, they are grossly abnormal, flattened, and covered with only an exceedingly thin layer of squamous-like cells in contrast to the abundant surface presented by the normal epithelial covering (2, 33, 34, 44, 45, 46). The absorptive and barrier functions of the heavily irradiated intestine are, of course, altered, but not to the extent that one would anticipate if villi were truly denuded of epithelium. Recent studies in which the exteriorized small intestine of the rat was irradiated with 2000 R while the body was shielded show that radioactive iron fails to "leak" into the lumen of the apparently denuded bowel and is in fact absorbed through it. On examination of histological sections, it was found that the luminal surface of the small intestine was covered with a very thin layer of flattened epithelium. This would be dislodged unless exquisite care were taken when obtaining specimens and preparing sections for study (44).

Decreased absorption of bile salts, glucose, thiamine, pyridoxine, and the divalent cations, calcium and strontium, by the heavily irradiated intestine has been observed in studies utilizing rats (39, 40, 41, 45, 46, 47). Absorption of fat, protein, and vitamin B_{12} is variably altered (45).

In patients receiving radiation therapy to the abdomen, decreased fat absorption has been observed very early in the course of therapy. Usually this disturbance has proved to be reversible (45, 48). In some patients, however, the diarrhea that developed during therapy persisted for months or years and was ultimately followed by either chronically recurrent diarrhea or by the development of the malabsorption syndrome (49). Malabsorption (usually reversible) of sugars, iron, and vitamin B_{12} has also been observed in patients receiving radiation therapy over the abdomen (48, 49, 50). Although the doses were fractionated in these clinical studies, total radiation doses delivered to the abdomen were considerably larger than the single doses usually administered to the entire body of animals in experimental studies of the G.I. syndrome.

Considered in the context of treatment of irradiated casualties, failure to absorb nutrients during the period represented by the G.I. syndrome is a minor consideration. Man can tolerate food deprivation for such intervals without dire consequences. Effects of altered absorption and resorption on water and electrolyte balance, however, have potentially much more serious implications.

VIII. WATER AND ELECTROLYTE LOSS

Many published reports document the maintenance of adequate, though not optimal, hydration and electrolyte balance in various species of experimental animals until shortly before death from the G.I. syndrome (2, 51). Except for maintaining the relatively modest normal minimum rate of sodium movement into the lumen of the large bowel, water and sodium transfer is decreased in both directions across the intestinal epithelium during the early phase of the G.I. syndrome (40). In contrast, the abrupt transition to a moribund condition that characterizes the terminal phase of the G.I. syndrome is accompanied by severe disturbances of water and electrolyte balance (2, 14, 28, 45, 51, 52, 53), and fluid and electrolyte replacement, even with whole blood, are ineffective. The sudden onset of intractable fluid and electrolyte imbalance has been observed in patients receiving therapeutic irradiation of the abdomen as well as in experimental animals (45, 48, 49). If the patients receive vigorous supportive therapy aimed at restoring the balances and counteracting shock, survival may be prolonged and ultimate recovery may be possible providing the ensuing hazards related to hematopoietic failure can be managed successfully. With respect to fluid and electrolyte loss it is important to remember that these are exaggerated in endotoxin shock, unusually extensive leakage of fluid through the damaged epithelium being the rule. Treatment to reopen the microcirculation must be accompanied by vigorous fluid replacement to correct fluid loss and compensate for the increased size of the vascular bed when vasospasm is alleviated.

IX. INTESTINAL FLORA

The bacterial flora is an important determinant of mucosal structure in the intestine of normal animals as well as in animals with disturbed gastrointestinal physiology (18, 54, 55, 56, 57). Sprinz has shown that the rapid rate of cellular proliferation characteristic of the epithelium of the mouse ileum "is due, at least in part, to the presence of a living bacterial flora. In the absence of such flora, i.e., in the germ-free animal, the renewal process proceeds at a significantly slower pace." In his studies, the flora was found to have a profound influence on structure and population dynamics of both the lamina propria and the epithelium (18).

It is clear that the G.I. syndrome, although considerably modified, does develop in germ-free animals providing the radiation dose is great enough. Wilson, Bealmer, and Matsuzawa observed that mitosis of crypt cells ceased after a single dose of 3000 R in both germ-free and conventional CFW mice. In the germ-free mice, however, loss of cells from the crypts and denudation of villi occurred more slowly than in the conventional mice (Table 3). Nevertheless, death did occur shortly after the denudation was complete. Mean survival time for conventional mice was 3.5 days, typical of the G.I. syndrome. The germ-free animals, however, had a mean survival time of 7.3 days, well into the period during which death would otherwise be attributed to hematopoietic failure (17). Not all authorities agree that this is the true G.I. syndrome (2, 14).

Ex-germ-free mice that had been fed cecal contents obtained from their normal counterparts (5 weeks before irradiation) survived 4.6 days, and mice contaminated with a pure culture of Streptococcus faecalis, Escherichia coli or Pseudomonas aeruginosa 24 hours before irradiation survived 6.9, 6.2, and 5.4 days respectively (17). In short, under the conditions of the experiment, the germ-free state was associated with longer survival, even though infection of the gastrointestinal tract with cecal organisms was induced prior to irradiation.

In men as in mice, much remains to be learned about the relationship between bowel function and bowel flora, and the role of flora in the body's over-all vital economy. Dubos has focused attention on this problem through studies of the indigenous microbiota of several strains of mice. He has taken issue with the concept of "normal microbiota," finding the phrase "merely denotes a multiplicity of microbial types which happen to be associated

Table 3

GASTROINTESTINAL SYNDROME IN GERM-FREE AND CONVENTIONAL MICE

(3000 R)[1]

Variable	Conventional	Germ-Free
LD_{50}	660 ± 25 R	705 ± 8 R
Time to 50% reduction in crypt cells	18 hr	36 hr
Time to 50% reduction in villus cells	2 days	4 days
Onset of hemorrhagic diarrhea	2.7 days	5.5 days
Mean survival time	3.5 days	7.3 days

[1] Data from Ref. 17.

with a given animal population, but it does not imply that such organisms are necessarily present in other populations of the same animal species." He has demonstrated that "(a) the whole gastrointestinal tract throughout life harbors an abundant bacterial flora, the composition of which is characteristic for each section of the tract, and (b) some bacterial species are intimately connected with the wall of the various organs." He further demonstrated that in various mouse colonies studied, these indigenous organisms may account for certain prominent characteristics that appear to be genetically determined (56, 57, 58).

Information about the interrelationships between normal flora and pathogenic flora in the gastrointestinal disease is even more fragmentary than that about the normal flora in the normal animal (56, 57, 59, 60, 61). Widespread use of antibiotics in clinical medicine has demonstrated that interference with this relationship may produce profound effects (62). The same may be said of the virus population of the G.I. tract. It seems reasonable to suppose

that in the debilitated (e.g. heavily irradiated) subject, the consequences of such disturbance might exceed those in otherwise uninjured subjects.

Techniques such as those developed by Dubos and his colleagues are essential if one would study the indigenous flora of normal animals. The concepts these investigators have developed are clearly of profound significance (56, 57, 58). The organism and its flora evolve together, and the gastrointestinal flora can exert great influence on growth and development, disease resistance and on general health. One hopes that the implications of these concepts with respect to the G.I. syndrome in irradiated animals will be explored more extensively than they have been so far. This is not to belittle in any way the many careful bacteriological studies that have been done using conventional bacteriological techniques (2, 61, 62, 63, 64). These have been widely reported and a comprehensive review of them is beyond the scope of this report. A fresh approach to the problem, however, taking advantage of newer techniques and concepts, would almost certainly be fruitful.

There is no definitive information about the influence of intestinal flora on the shedding of epithelium during the G.I. syndrome. It has been observed that the mucosa often sloughs off in sheets in the irradiated conventional animal whereas it is lost through the orderly "migration" process in irradiated germ-free animals and in conventional animals treated with colchicine to arrest mitosis of crypt cells (17, 24). In dogs, if a loop of intestine (not sterile) is surgically isolated (Thiry-Vella fistula) from the rest of the gastrointestinal tract prior to irradiation so that its circulation remains intact but intestinal contents do not pass through it, the effect of radiation on epithelial cell proliferation is not altered, but the severity of mucosal erosion, bleeding, flattening of villi, and infiltration with inflammatory cells is significantly decreased in the isolated loop. Hiatt and Warner, who carried out these experiments, feel that the differences observed were attributable not to bacteria or motility but probably to presence or absence of bile and proteolytic enzymes (42).

Bacterial endotoxins may act directly on cells, disrupting membranes and subcellular structures including lysosomes. It is possible that they participate in accelerating the loss of epithelium (65). In monkeys irradiated with X-ray doses large enough to elicit the G.I. syndrome, ulcers were observed in the body of the stomach, small intestine, and colon of some of the animals. This occurred rarely in the small intestine, but 33 of 45 animals had colonic ulceration, predominantly in the ascending and first part of the transverse colon. Gastric ulceration occurred with

greater frequency following increasing radiation doses (1500 to 7500 R) and in each dosage group, animals with ulcers died sooner. There was bacterial invasion and hemorrhagic necrosis of mucosa in both gastric and colonic ulcers. The rare occurrence of ulcers in the small intestine, which normally has scanty bacterial flora, in contrast to their frequent occurrence in the colon was felt to be attributable in large part to the large numbers of bacteria, the presence of severe neutropenia, and nearly complete suppression of immune processes (33).

X. SEPTIC SHOCK

Disseminated infection may occur as the terminal event in the G.I. syndrome and, in fact, death is often attributed to that complication (2, 14, 28, 45). In the presence of severe - nearly absolute - neutropenia, failure of antibody production, thrombocytopenia, and increased vascular permeability, the heavily irradiated animal has little reserve to call on in combating infection. It has frequently been observed that the immediate cause of death under such circumstances is an overwhelmingly disseminated infection with one of the animal's commensal organisms that would not ordinarily be considered pathogenic. They frequently come from the intestinal tract, but may also originate elsewhere in the body (59, 60, 61). Once released into the circulation, the infection is fulminating.

Endotoxin is present in the cell walls of all gram-negative rods, which are commonly found in the intestinal tract. If large numbers of these bacteria are suddenly disrupted, enough endotoxin may be released to cause endotoxin shock (66). The gravity of this complication is well documented (debilitated patients are especially susceptible). In a recent review of 59 cases of gram-negative bacteremia studied in one hospital, 70% of the patients who developed hypotension (shock) died, in contrast to 47% of those whose blood pressure remained normal (67). The similarities between the terminal phase of septic or endotoxin shock and the G.I. syndrome are summarized in Table 4.

Eddy and Casarett suggest that the altered vascularity they observed in preparations of perfused intestines from irradiated rats may result in "serious impairment of the regenerative capability through reduction in functional integrity of supporting vasculature" (32). The possible relationship of these changes to endotoxin shock appears to have been overlooked. Such an oversight is hardly surprising, for, in general, application of newer knowledge of the physiology of endotoxin shock appears not to have been exploited by investigators concerned with treatment of acute radiation injury.

The effects of endotoxin in irradiated animals have been studied by a number of investigators, but most of the research has been concerned with the use of endotoxins as radiation-protective or therapeutic agents (2) The rationale for these approaches is the "stimulating" effect of endotoxin on hematopoietic tissue. One recent report describes the interaction of radiation and endotoxin, but the experiments were designed along

Table 4

COMPARISON OF TERMINAL PHASE OF G.I. SYNDROME AND ENDOTOXIN SHOCK (DOGS)*

	G.I. Syndrome	Endotoxin Shock
Clinical Picture	sudden onset of disturbed sensorium; hypotension; rapidly lethal	sudden onset of disturbed sensorium; hypotension; LD_{95} dose of endotoxin causes death in a few hrs; LD_{50} dose in 24 hrs.
Microcirculation	microcirculatory failure in viscera, skin; fluid and electrolyte loss into intestine	microcirculatory failure in viscera, skin; fluid and electrolyte loss into intestine (greater than loss in hemorrhagic and traumatic shock).
Histology of intestinal epithelium	flattened, "denuded" villi; few abnormal giant cells; early signs of restitution of mitosis	disruption of subcellular structures (mitochondria, lysosomes); early destruction of cells and hemorrhagic necrosis of mucosa within few hrs. (all secondary to ischemia; villi not denuded).
Biochemical changes	acidosis; hypokalemia	acidosis; hypokalemia

* Terminal phase. In man, kidney is more prominently affected in early stages of endotoxin shock.

the lines of those classically used in studying the immune response to toxins. The experiments, although interesting in their own right, are not pertinent to the possible importance of endotoxin shock as the immediate cause of death in the gastrointestinal form of the acute radiation syndrome (68).

Highly refined techniques for studying the dynamics of the circulation during shock have been developed in the surgical and cardiovascular laboratories where this problem is studied (66, 69, 70). It would appear that these techniques might be applied to good advantage in studying animals that develop the G.I. syndrome. The dog is remarkably similar to man with respect to the physiology of shock and would probably be the experimental animal of choice.

Animals dying as a result of the G.I. syndrome often show evidence of beginning regeneration of intestinal epithelium, and this regeneration, once it commences, can proceed with remarkable rapidity. Restitution of intestinal architecture was nearly complete within two weeks in dogs subjected to supralethal doses of radiation and kept alive by supportive therapy and bone marrow transplants (28). It is clear, however, that just as a recovery trend became established in the intestine, death from some ill-defined cause intervened. The possibility that the terminal event or terminal phase in many instances was endotoxin shock deserves serious consideration, for early diagnosis and skillful clinical management may save the lives of many patients developing this complication (66, 67).

It has been recommended that especially susceptible groups be made resistant to endotoxin shock (66). Patients such as paraplegics who have chronic gram-negative bacterial infection and repeated episodes of bacteremia become resistant to endotoxin shock; resistance can also be induced in experimental animals (66). Endotoxin shock might also prove to be amenable to therapy with some of the newer pharmaceutical agents. Lillehei has shown that endotoxin shock in the dog (until fairly recently found to be refractory to treatment that proved effective in hemorrhagic or traumatic shock) can be reversed if dibenzyline and fluids are given as soon as the condition is recognized (70).

Results of recent clinical and experimental studies, taken together, strongly suggest that if treatment for hematopoietic failure were available (including appropriate, judicious use of antibiotics), and if endotoxin shock could be prevented or treated promptly with the aid of newer medications such as dibenzyline, the G.I. syndrome might have a less bleak prognosis than it has at present.

XI. LOCAL IMMUNITY

The importance of local immune responses against gastrointestinal pathogens and their implications with respect to the treatment of heavily irradiated patients appear to deserve fresh appraisal. The intestinal lymphoid tissue is, of course, largely destroyed by radiation doses producing the G.I. syndrome. In unirradiated patients, however, development of coproantibodies against intestinal pathogens has been observed to be separated from production of circulating antibodies with respect to time of appearance, type of antibody, and probably site of origin. In cholera, for example, coproantibodies appear first and represent a highly effective defense mechanism (71). Injection of immune serum or passive immunization of the intestinal tract, if it could be accomplished, might prove to be therapeutically useful alone or as an adjunct to antibiotic therapy.

One intriguing approach to immune therapy of intestinal disease is exemplified by the induction of urease immunity as a means of decreasing the amounts of ammonia produced by urease from certain intestinal bacteria (72, 73). Visek and his colleagues propose that ammonia may be of considerable importance in producing the changes observed in heavily irradiated animals, and they have demonstrated the beneficial effects of immunity to urease in irradiated mice (72, 73).

XII. ABSORPTION OF TOXIC INTESTINAL CONTENTS

It has been suggested that release of proteolytic enzymes (or products of their action on intestinal contents and damaged epithelium) into the circulation might account for some of the terminal deterioration in the condition of irradiated animals (1, 2, 33, 34, 42). Diversion of pancreatic secretions from the intestinal tract has been observed to alter the histological picture of the irradiated intestine (74), but the precise role of the pancreatic secretions in causing acute intestinal radiation lethality is poorly understood (2, 14, 34, 37, 45). In general, secretory activity of digestive glands tends to be reduced following exposure to large doses of radiation (37). It has been shown, however, that the barrier to absorption of large molecular weight compounds remains intact in irradiated animals (74, 76).

XIII. G.I. SYNDROME AND DRUG TOLERANCE

Aside from problems related to absorption of medications or their effects as local irritants, the gastrointestinal syndrome appears not to be associated with markedly altered tolerance for commonly prescribed medications. Some of the radiation-induced morphological changes in subcellular structure observed in tissues such as liver that are, in the normal animal, active sites of drug metabolism might lead one to expect that detoxication would be impaired. Available evidence suggests, however, that when such impairment occurs it is of relatively minor importance in the G.I. syndrome. Mitochondria, for example, may be considerably distorted without demonstrating significant change in their oxidative capacity. When the irradiated experimental animal shows altered tolerance for parenterally administered drugs such as sedatives and analeptics, it is difficult to determine whether the observed change represents an alteration in the response mechanism of the recipient, defective detoxication, or some combination of metabolic alterations (77, 78, 79, 80, 81, 82, 83). As a rule, radiation accident casualties and patients receiving therapeutic irradiation do not have abnormal requirements for, or reactions to, medications.

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Five patients with acute leukemia refractory to other therapy were treated by whole body exposure to ^{60}Co γ-radiation followed by bone marrow transplantation. The doses ranged from 1400 to 2000 R delivered at dose rates varying from 33 R to 144 R per hour. No severe intractable gastrointestinal disturbance occurred following exposure at 33 or 54.6 R per hour, but exposure at 144 R per hour (one patient) was followed by gastrointestinal symptoms that were moderately difficult to manage clinically. When the patient died (from hepatitis) three weeks later, virtually complete restoration of normal intestinal morphology was found. E. coli septicemia was a frequent terminal complication.

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In March, 1962, a family consisting of a father, a pregnant mother, a 10 year old son and a three year old

daughter moved into a house in which the previous occupant had left a 5 curie lead-enclosed ^{60}Co source. The family had been asked to look after the object but they did not know what it was. Shortly after the family moved into the house, the source, in some way, was removed from the lead capsule. The 10 year old boy carried the unshielded source in the pocket of his trousers for about a week. The mother then placed the source in a drawer in the kitchen. In April the grandmother joined the family in the house. All five persons were exposed to the γ-radiation over a period of approximately 5 months. One by one the family members became ill and were hospitalized. The boy died on April 29, the mother on July 19, the three year old girl died in mid-August and the grandmother in mid-October. The clinical and laboratory findings are presented. The presenting symptoms were those of infection and hemorrhage; the findings those of severe bone marrow hypoplasia. The cause of the injury was not suspected until after the boy and his mother had died. Precise dosimetry was not possible, but best estimates indicate that the family received γ-ray doses ranging from (approximately) 1200 R to 4700 R during the protracted period of exposure.

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Two series of Beagles were exposed to 1000 kVp x-rays. The first series consisted of animals given single-session, whole-body irradiation, dorso-ventrally, of 450 R, 600 R or 700 R at 1 R/min, or 400 R and 600 R at 11.4-12.2 R/min. In the second series Beagles were exposed bilaterally to 150 R - 400 R whole-body, 970 R - 2425 R upper body or 400 R - 1100 R lower-body in single session at 50-65 R/min or by fractionation at 12, 24 and 48 hour intervals at 50-65 R/min or 8-12 R/min. All were midline air exposure doses (MAED). Sham-irradiated animals were included for comparison. The estimated median lethal midline air exposure dose for the dorso-ventrally irradiated dogs was 657 R ± 30 R (S.D.) at 1 R/min and 502 R ± 22 R at 11.4 - 12.2 R/min. The regression lines were parallel. The estimated relative potency was 1.3 for 11-12 R/min and 2.1 for 50-65 R/min (bilateral)

irradiation in comparison to 1 R/min as the standard. Survival time after exposure was inversely related to dose intensity as well as total dose. Shielding influenced lethality in relation to location of radiosensitive body organs and systems. The 60 day median lethal doses in the second series were 308 R ± 18 R, 878 R ± 9 R and 1998 R ± 48 R with relative shield effectiveness of 1.0, 2.8 and 6.5 for whole-body, lower-body, and upper-body irradiation respectively. In addition to intensity of irradiation, fractionation, or the interval between exposures i.e. 12, 24 or 48 hours, was an important determinant of lethality. For whole-body irradiation at the $LD_{50/60}$, fractionation at 48 hours was effective in reducing lethality; the relative effectiveness of 12 and 24 hour fractionation was considerably lower. The influence of radiation intensity or the interval between exposures was also reflected by the changes in hematologic indexes. Higher intensity irradiation was more effective in depressing various white blood cell components. The effectiveness ratio for hematological depression for 11-12 R/min vs 1 R/min radiation was 1.3 which is identical with the ratio for acute lethality production in the Beagle. The greater effectiveness of some fractionation schedules over others or over single exposures when selected portions of the body were irradiated suggests that cyclic variations in metabolic activity of specific cell types influence the synergism, augmentation, or diminution of the responses. (Authors)

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The duodenum of mice exposed to γ-irradiation recovers completely, and the mice live beyond the critical 3½- to 6-day period of the "intestinal syndrome."

The duodenum of mice exposed to fission neutrons is severely damaged, and less than 50% live beyond the 6-day period. Damage to the small intestine plays a dominant

role in these early deaths. There is a close relationship between the degree of intestinal damage, generalized bacterial infection, and time of death.

Irradiation with fission neutrons produces a high percentage of irreparable chromosome breaks and leads to a prolonged delay in cell division. The comparison of duodenal damage and recovery rate suggests an RBE (n/γ) greater than 6 for intestinal sensitivity. (Authors)

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Intestinal weight and intestinal length were measured in normal CF No. 1 female mice and in similar mice that had been exposed to single whole body doses of fission neutrons or ^{60}Co gamma radiation. Total doses throughout the lethal and supralethal range (highest dose 3000 rads) were given. Although previous studies had shown that the n/γ RBE for hematological recovery (spleen colony assay) is approximately two, fission neutrons proved to be more than four times as effective as ^{60}Co γ-radiation in producing intestinal weight loss.

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The major radiation accidents are described, along with the therapeutic use of whole-body irradiation and tissue transplantation in man. Treatment and problems for future study are emphasized. The discussion following the various sections is well and fully reported and is a particularly valuable part of the publication. These accidents all represent radiation injury of civilians and as such are valuable source material to physicians, health physicists and others concerned with the management of accidental acute radiation injury, as well as to those interested in military medicine.

10. Report of United Nations Scientific Committee on the Effects of Atomic Radiation. General Assembly, Official Records Seventeenth Session, Supplement No. 16 (A/5216), United Nations, N. Y. (1962).

This report, compiled by the Scientific Committee on the Effects of Atomic Radiation (U. N.), reviews the knowledge current at the time of publication (1962) about effects of radiation on man and his environment. Descriptions of some major radiation accidents are included in the section on Acute Radiation Injury in Man.

11. Thoma, G. E. Jr. and Wald, N.
The Diagnosis and Management of Accidental Radiation Injury.
J. Occup. Med. 1: 421-447 (1959).

The authors describe concisely the seven major criticality accidents that had occurred at the time of writing and present a classification of five degrees of radiation injury based on the clinical and laboratory findings in the various radiation casualties in those accidents, in casualties of atomic bombing and in patients receiving radiation therapy. Hypothetical cases are described to illustrate the various injury groups. A profile scoring method is then developed, based on 1. time of onset and duration of initial clinical symptoms, 2. time of onset and duration of clinical signs and symptoms in the "manifest illness stage", and 3. abnormal hematological changes expressed as increases above and decreases below the "universal mean" (as defined in Standard Values in Blood, Part 1 of AIBS - NRC Handbook of Biological Data, W. B. Saunders Co., Philadelphia, 1952, E. C. Albritten, Ed.). Daily logging of the integral and cumulative profile scores provides a valuable guide to diagnosis and prognosis in individual cases. Examples of the use of the profile scoring system are presented and discussed with emphasis on the reassuring observation that, "... despite the disturbing physical complexity of nuclear criticality accidents, the key procedures for clinical evaluation of resultant injury are such familiar ones as a detailed medical history, thorough physical examinations and accurate blood counts."

12. Dunham, C. L., Cronkite, E. P., LeRoy, G. V. and Warren, S.
Atomic Bomb Injury: Radiation.
J. Am. Med. Assoc. 147: 50-54 (1951).

The authors describe the forms of the acute radiation syndrome observed following total-body exposure to large doses of ionizing radiation and correlate the clinical observations with approximate dose and with prognosis.

13. Oughterson, A. W. and Warren, S., editors
Medical Aspects of the Atomic Bomb in Japan.
McGraw Hill, New York (1956).

This volume, part of the National Nuclear Energy Series, is a comprehensive report on the clinical and pathological changes observed in Japanese victims of the atomic bombing of Hiroshima and Nagasaki during World War II.

14. Sullivan, M. F., editor
Mechanism of Intestinal Radiation Death. Panel Discussion
In: Gastrointestinal Radiation Injury
Excerpta Medica Foundation, N. Y. pp. 351-373 (1968).

Various aspects of the mechanism of intestinal radiation death were summarized by selected participants in the symposium (V. P. Bond, moderator, S. Hornsey, S. Lesher, C. C. Lushbaugh and J. W. Osborne). This was followed by discussion. A lively exchange of learned opinions is fully reported. The issue on which opinions varied most strongly was the relative importance of interrupted cellular proliferation and water and electrolyte loss in causing acute intestinal radiation death. There is considerable discussion of radiosensitivity and repair vs. recovery phenomena and of the high RBC of neutrons when intestinal injury is the test system. The multiple contributions of bile to the deranged intestinal physiology following irradiation is concisely but comprehensively reviewed.

15. Lesher, S.
Effects of Single-Dose Whole-Body Irradiation on the Mouse Duodenal Crypt Cells.
In: Gastrointestinal Radiation Injury
M. F. Sullivan, Ed., Excerpta Medica Foundation, N. Y. pp. 103-109 (1968).

Techniques applied in studying the cell cycle of intestinal crypt cells are discussed briefly and illustrated by results from an experiment in which they were applied. Following a single whole-body exposure to 300 R of ^{60}Co γ-radiation, cells in all phases of the cell cycle are damaged. Cells in some phases, however, are either more sensitive (e.g. G_2 and M) or the damage is repaired before the cell attempts division and becomes detectable. The importance of the in vivo environment in studying compensatory responses of the irradiated crypt cell population is emphasized.

16. Fry, R. J. M., Lesher, S., Kisieleski, W. E. and Sacher, G.
Cell Proliferation in the Small Intestine.
In: Cell Proliferation. Lamerton, L. F. and Fry, R. J. M., editors. F. A. Davis Co., Philadelphia
pp. 213-233 (1963).

This paper is concerned with some of the problems involved in determining the fate and life span of the mucosal cells of the small intestine and the use of the cells of the crypt of Lieberkuhn in the study of the cell cycle and cell proliferation rate. Various methods used in arriving at estimates of duration of various parts of the cell cycle, e.g. "percent mitoses labeled" method, are discussed with reference to specific data obtained by the authors or others.

17. Wilson, R., Bealmear, P. and Matsuzawa, T.
Acute Intestinal Radiation Death in Germfree and Conventional Mice
In: Gastrointestinal Radiation Injury
M. F. Sullivan Ed., Excerpta Medica Foundation, N. Y.
pp. 148-157 (1968).

Conventional and germfree CFN mice were exposed to a single dose of 3000 R of x-rays. Some of the germfree mice were maintained germ-free, others were given a standard inoculum (in diet and water) of S. faecalis, E. coli, P. aerugenosa or cecal contents obtained from conventional mice five weeks before irradiation. Mean survival time was greater in all germfree mice, even in the monocontaminated groups. It was longest in the germfree mice that remained germfree. Graphed and tabulated data show that the rate of loss of intestinal mucosa was much faster in conventional mice. Life span of

epithelial cells estimated for the various experimental groups were 2.1 days in conventional mice, 4.3 days in germfree mice, and intermediate lengths for the monocontaminated mice. In the mice receiving cecal contents, the estimated epithelial cell life span was 2.7, the shortest of the deliberately contaminated group.

18. Abrams, G. O., Bauer, H. and Sprinz, H.
Influence of Normal Flora on Mucosal Morphology and Cellular Renewal in the Ileum. A Comparison of Germ-Free and Conventional Mice.
Lab. Invest. 12: 355-364 (1963).

By comparison of germ-free and conventional mice, many of the morphologic characteristics of the ileal mucosa ordinarily recognized as "normal" were demonstrated actually to develop in response to the presence of the bacterial flora of the natural environment.

Autoradiographic study of the ileum at various times after administration of tritiated thymidine to the two groups of mice revealed that cellular renewal rates in the mucosa are likewise sharply influenced by the normal microbial flora. The rate of turnover of the ileal epithelium in the germ-free state was found to be significantly lower than in the presence of the conventional flora. Although not measured as precisely, turnover of cells in the lamia propria and Peyer's patches appeared to be affected similarly by the living flora.

The possible implications of these effects of the flora were discussed and the concept of the intestinal mucosa as a dynamic system was emphasized. (Authors)

19. Patt, H.
Cell Turnover and Mammalian Radiosensitivity.
Cell Tissue Kinet. 1: 81-88 (1968).

In this carefully reasoned discussion of radiation-induced disturbance of kinetics of cellular proliferation in various tissues, the author considers bone marrow and intestinal modes of radiation death, pointing out that they may overlap. Their relative contributions to lethality following radiation doses in the $LD_{50/30}$ range depends somewhat on age in experimental animals (mice) and on species (rat being more sensitive than the mouse to the intestinal mode of death). He urges 1. caution in acceding to the assumption that death of stem cells bears a simple relationship to death of the organism, and

2. the aquisition of more quantitative information about the level of mature functional cells needed for survival. He states, "In cell renewal systems there is a 'pull' rather than a 'push' in the sense that cells are produced apparently to replace functional cells that are lost or die. It is, therefore, appropriate to focus on the functional cell in an analysis of the behavior of such systems to radiation-induced perturbation."

20. Lesher, S.
Compensatory Reactions in Intestinal Crypt Cells after 300 Roentgens of Cobalt-60 Gamma Irradiation.
Radiat. Res. 32: 510-519 (1967).

A single 300-R whole-body ^{60}Co γ-ray dose markedly changes the proliferative cells in the mouse duodenal crypts. Cells in all phases of the generation cycle were affected as follows: (1) Most cells in mitosis completed division, but the process was prolonged; (2) cells in G_2 were blocked in G_2 for approximately 4 1/4 hours and then experienced difficulty with mitosis; (3) cells in S continued DNA synthesis, but at a reduced rate (however, after synthesis was completed they appeared to move through G_2 and divide); and (4) movement of G_1 cells to S was retarded. During the recovery phase, when killed and less-damaged cells were being replaced, the repopulation of the crypts and the return to the normal steady-state relationship which exists between the proliferative and non-proliferative cells of the intestinal epithelium were hastened by two compensatory mechanisms: (1) an acceleration of the generation cycle and (2) an increase in the number of cells in the proliferative compartment. (Author)

21. Lipkin, M., Sherlock, P. and Bell, B.
Cell Proliferation Kinetics in the Gastrointestinal Tract of Man. II. Cell Renewal in Stomach, Ileum, Colon and Rectum.
Gastroenterology 45: 721-729 (1963).

Cell proliferation rates and the length of the various phases of the cell cycle were estimated for proliferating epithelial cells of stomach, ileum, colon and rectum in three patients who already had gastrotrostomy, ileostomy or colostomy. Tritiated thymidine was injected intravenously and mucosal biopsy specimens were obtained serially for autoradiographic studies. Mean generation time was approximately one day for epithelial cells of stomach, ileum, colon and rectum, indicating that gastrointestinal epithelial cells are produced at the

rate of approximately one cell per 100 cells per hour. The G_2 portion of the cell cycle was about 2 hours, and DNA synthesis phase was 9 to 14 hours.

22. Sherman, F. G. and Quastler, H.
DNA Synthesis in Irradiated Intestinal Epithelium.
Exper. Cell Res. 19: 343-360 (1960).

Autoradiographic preparations of sections of ileum were obtained serially from mice that received ^3H-labeled thymidine at various times following whole body exposure to 0, 400, 800 or 2500 rads of X-rays. These preparations were studied to determine the effects of irradiation on DNA synthesis and cell proliferation and to obtain further information about the importance of interrupted proliferation of intestinal epithelial cells as a cause of acute intestinal radiation death.

Irradiation resulted in decreased incorporation of thymidine by intestinal crypt cells, the decrease being proportional to radiation dose. The initial phase of the decreased incorporation was a block of DNA synthesis (cells in S phase of cell cycle). Most of the affected cells did not die, but matured precociously and migrated out of the crypts onto the villi. DNA synthesis was resumed before cell division, the crypt cells in heavily irradiated mice completing one or two cycles of synthesis without dividing. Migration of cells along the villi is influenced relatively little by irradiation as shown by cellular depletion of crypts as their cells migrate up the villi during the period when there is little or no DNA synthesis.

23. Lesher, S., Fry, R. J. M. and Kohn, H. I.
Influence of Age on Transit Time of Cells of Mouse Intestinal Epithelium.
Lab. Invest. 10: 291-300 (1961).

Transit time of epithelial cells was found to be different in three regions of the small intestine (duodenum, jejunum and ileum) in mice and was independent of the length of the villi. The rate at which labeled cells traverse the villi decreased with age in all regions, but differences in "pressure" from the crypt population could not account for the differences in rates of migration along villi.

24. Hampton, J. C.
The Effects of Nitrogen Mustard on the Intestinal Epithelium of the Mouse.
Radiat. Res. 30: 576-589 (1967).

Microscopic and electron microscopic studies of segments of ileum from mice killed serially following four daily injections of nitrogen mustard (50 μg per 20 gm body weight) are described and compared with observations of the ileum of other mice following 3000 rads of X-rays or daily injection of colchicine. Colchicine arrested mitosis in metaphase for 4-5 days; X-rays and nitrogen mustard both interrupted mitosis by their action on cells in the pre-mitosis phase (G_2) of the cell cycle. (They also resulted in decreased fat absorption.)

Effects of nitrogen mustard and X-rays were closely similar and could be observed as disruption of subcellular architecture on electron micrographs of all epithelial cells, i.e. not only in dividing cells. Colchicine had little or no effect on subcellular structures other than the spindle. Loss of epithelial covering of villi and bacterial invasion of crypts did not occur in the ileal epithelium following colchicine as it did following exposure to the other two agents. Electron micrographs are presented to illustrate the types of changes observed.

25. Lamerton, L. F. and Courtenay, V. D.
The Steady State Under Continuous Irradiation.
In: Dose Rate in Mammalian Radiation Biology
TID-4500, Conf. 680410
DTIE, Oak Ridge, Tenn.

Analyses of data from the authors' laboratory and from other laboratories are presented to demonstrate the way in which maintenance of the steady state by renewal tissues under continuous irradiation depends upon 1. the cellular radiosensitivity under continuous exposure at low dose rates and 2. the extent to which tissue can adapt to the continuous irradiation. Responses of intestinal epithelium, bone marrow and testicular epithelium under continuous irradiation in vitro are compared with respect to the nature of the physiological controls over their cell production and the intrinsic radiosensitivity of the proliferating cells.

26. Lesher, S., Lamerton, L. F., Sacher, G. A., Fry, R. J. M., Steel, G. G. and Roylance, P. J.
Effect of Continuous Gamma Irradiation on the Generation Cycle of the Duodenal Crypt Cell of the Mouse and Rat.
Radiat. Res. 29: 55-56 (1966).

Rats (120 gm) and mice (20 gm) were placed in separate cages and exposed to continuous gamma radiation from ^{60}Co. Rats received 50 rads/day for 12, 35 or 105 days; mice for 12 or 35 days. At the end of the exposure period, tracer doses of ^{3}H thymidine were injected and some animals were killed at closely spaced intervals from 1/2 to 20 hours thereafter. Similar injections were administered to non-irradiated control animals. Histological studies as well as counts of mitotic and labelled cells in intestinal crypts of each of three sections of each animal's upper small intestine were carried out to evaluate the effects of irradiation. Duration of the various stages of the cell cycle were calculated from the percent labeled mitotic figures found at each sampling interval. The sequence of events observed in the intestinal crypts of continuously irradiated animals consisted of 1. retardation of cell cycle after 1 day of exposure, 2. shortening of the generation cycle by approximately 20%, 3. return to nearly normal values by 35 days in the mouse and 105 days in the rat.

27. Hornsey, Shirley
The Recovery Process in Organized Tissue
In: Radiation Research 1966, G. Silini, editor.
North Holland Publishing Co., Amsterdam pp. 587-603 (1967)

Using the split-dose technique (in which the size of a second dose needed to produce a given end-point is presumed to be proporticnal to the degree of recovery from an initial dose) the author found a large difference between the $LD_{50/4}$ for single doses and the $LD_{50/4}$ for doses separated by more than 2 hours. The survival curve was characterized by a broad shoulder, indicating that the animals could repair intestinal damage from relatively large doses (death by the fourth day, the end point, being acute intestinal death). An effect of dose rate was found over the range 100 rads/min. to 6 rads/min. The high value for $D_2 - D_1$ for acute intestinal death (300 rads) would mean that the level of cell killing tolerated by the intestine was much greater than in the haematopoietic system. An alternative explanation, favored by the author, would be that the two tissues

have different types of survival curves. Survival curves in other tissues are also discussed in this paper.

28. Hager, E. B., Ferrebee, J. W. and Thomas, E. D.
Damage and Repair of the Gastrointestinal Tract after Supralethal Radiation.
Radiobiol.-Radiother. 4: 1-12 (1963).

The authors describe changes observed in structure and function of the gastrointestinal tracts of 55 dogs following whole body exposure to 1800-2400 R (midline air dose) of ^{60}Co γ-radiation followed by infusions of bone marrow to all but five dogs and antibiotics to all but two (to prevent death from hematopoietic failure). Replacement of fluid and electrolyte losses as necessary was also part of the supportive therapy. Doses ranged from 1800 R to 2400 R at dose rates of 2, 5, 7, 12 or 18 R per minute, total doses delivered in a single exposure except for 10 dogs who received 1800 R as three daily doses of 600 R.

Dose rate had a striking effect on the gastrointestinal symptomatology. A total dose of 1800 R administered as three daily doses of 600 R at a dose rate of 2 R per minute produced only mild symptoms and at autopsy 6-10 days after exposure, (death from sepsis and pneumonia) the gastrointestinal tracts were anatomically normal. Dogs that received 1800 R - 2400 R at dose rates of 12-18 R per minute developed severe gastrointestinal symptoms but with marrow transplants and supportive therapy many of them survived three weeks or longer. All but one of these showed either active regeneration or complete restoration of the intestinal epithelium at autopsy.

29. Elkind, M. M.
Dose-Survival Characteristics of Epithelial Cells of Mouse Intestinal Mucosa.
Radiology 91: 998-1000 (1968).

Dose-survival curves were established for clones of crypt cells from the jejunum of the mouse following x-irradiation of intestinal loops. D_o was 100 R. The cells were found to have a great capacity for repair of intracellular injury. Several different recovery patterns are described.

30. Loran, M. R. and Carbone, J. V.
The Humoral Effect of Intestinal Resection on Cellular Proliferation and Maturation in Parabiotic Rats.
In: Gastrointestinal Radiation Injury, M. F. Sullivan, editor, Excerpta Medica Foundation, N. Y. pp. 127-138 (1968).

The authors report results of their studies on the rate of cellular proliferation of intestinal epithelial cells in parabiotic rats, one partner of which had 10% of the ileum resected before or after parabiosis was established. They were able to demonstrate the existence of humoral factors which caused increased rate of proliferation, shortened life span of epithelial cells and alteration of DNA synthesis period and generation time. They postulate that there are two factors; one influences the rate of proliferation (number of proliferative cells), is self perpetuating (its effect persists in both partners if the parabionts are separated) and is not dependent on changes in the mitotic cycle. The second, which influences the length of the mitotic cycle, does not remain active in the non-operated parabiont if it is separated from its resected partner, i.e. it is "reversible".

31. Gangarosa, E. J., Beisel, W. R., Benyujati, C., Sprinz, H. and Prapont, P.
Nature of Gastrointestinal Lesion in Asiatic Cholera and It's Relation to Pathogenesis: Biopsy Study.
Am. J. Trop. Med. 9: 125-135 (1960).

The authors studied 19 specimens of intestine obtained by biopsy (Crosby capsule) from stomach, duodenum, jejunum, upper ileum and colon from patients with Asiatic cholera. Additional specimens from asymptomatic carriers served as controls. The histopathology of the enteritis, including the characteristics of cellular infiltration, flattening of villi and degenerative changes in epithelium (but not true denudation of villi) are described. Cell turnover was apparent as an increased incidence of mitotic cells in crypts. The non-specific nature of the lesion is emphasized.

32. Eddy, H. A. and Casarett, G. W.
Intestinal Vascular Changes in the Acute Radiation Intestinal Syndrome.
In: Acute Gastrointestinal Radiation Injury, M. F. Sullivan, editor. Excerpta Medica Foundation, N. Y. pp 385-395 (1968).

The histological and microangioradiographic changes were studied in the blood vasculature of the small intestine of rats killed at daily intervals or allowed to die spontaneously after a single 1460 R dose of whole-body X-irradiation to the temporarily exteriorized intestine sufficient to cause acute radiation intestinal death. There was an apparent relation between the degree and rate of development of radiation damage in the intestinal mucosa and the development of obstructive changes in the fine vasculature.

33. Wilson, S. G.
Radiation-Induced Gastrointestinal Death in the Monkey.
Am. J. Pathol. 35: 1233-1251 (1959).

Monkeys developed the gastrointestinal syndrome after whole-body exposure to ^{60}Co γ-ray doses of 1500 - 1700 R and died four - nine days post-exposure. Mean survival time was six days. Histological changes observed in tissue specimens obtained at the time of autopsy are described. Mucosa was atrophic throughout the gastrointestinal tract, but mucosal denudation was not seen. Ulceration of the gastric mucosa occurred in 13 animals; of colonic mucosa in 33 animals. Bacteria were characteristically found in association with the ulcers and it is suggested that they play an important role in ulcer production following exposure to supralethal doses of radiation. Mucosal atrophy in the intestine could be divided in four basic types: 1. "squamoid atrophy" in which the few epithelial cells were spread out in an extremely thin layer over the mucosal surface of the villi, 2. "squamoid atrophy with surface regeneration" in which only a few distorted epithelial cells remained, some of the aberrant cuboidal cells along the mucosal surface being mitotic (no mitosis in crypts), 3. "partial atrophy with surface regeneration" which resembled 2. (above) except that nests of cells having nearly normal morphology were present in the surface epithelium (but not in crypts) and 4. "basilar regenerative" in which cell production was being resumed and the regenerated glands were lined by hyperplastic epithelium. In some

cases this had progressed to complete re-epithelialization of the intestinal mucosa. Basilar regeneration occurred with greater frequency following decreasing doses. All four types of lesions were found in the small intestine; no type 3 lesions were found in the colon, where the type of regeneration appeared to be a function of survival time rather than radiation dose. Spotty hemorrhagic necrosis of mucosa was found to varying degrees throughout and there was marked edema of the lamina propria. Approximately a third of the animals showed nearly complete obliteration of the acinar pattern of the pancreas. The small blood vessels in the gastrointestinal tract are not described, but the cardiovascular system was said to be "singularly free of lesions."

34. Conard, R. A.
Some Effects of Ionizing Radiation on the Physiology of the Gastrointestinal Tract. A Review.
Radiat. Res. 5: 167-188 (1956).

The author describes the various effects of ionizing radiation on the physiology of the gastrointestinal tract, with reference to 77 well selected, published articles. His own studies on intestinal motility (showing that the motility was altered even when only the intestine was irradiated while the rest of the body was shielded) are among those cited to demonstrate parasympathetic stimulation at the level of the enteric ganglia. Other studies indicate that there may also be a radiation-induced imbalance of neurohumoral agents in irradiated rat intestine. Various attempts to modify the physiological effects of radiation are reviewed, including the correction of fluid and electrolyte imbalance in dogs given radiation doses of 1200-1500 R (which would normally produce death on about the fourth day). With therapy, animals could be kept alive into the second post exposure week, when recovery of gastrointestinal tract was nearly complete (autopsy findings).

35. Penner, A. and Klein, S. H.
The Pathogenesis of Experimental Dysentery Intoxication. Production of Lesions by Cerebral Circulation of the Toxin.
J. Exper. Med. 96: 59-69 (1952).

Pairs of dogs were studied in which the circulation of the brain of each dog, while isolated from its own systemic circulation, was supplied completely by the

visceral circulation of its partner which received toxin prepared from Bacillus shiga via the femoral vein. The toxin was shown to produce its systemic and local anatomical effects through a primary reaction in the brain. Gross anatomical and histological changes produced in viscera by the toxin are mediated by a vascular mechanism which is controlled by the sympathetic nervous system. Toxoid injections resulted in congestion, edema, and hemorrhagic lesions of the liver, gall bladder and intestines; superficial erosions of the mucosa of the small intestine and congestion and hemorrhagic medullary foci in the adrenals. Hemoconcentration was prominent, and there was also hyperglycemia and a decrease in serum chloride and CO_2 levels. Paralysis of the sympathetic nervous system at the myoneural junction, or in ganglia, by means of drugs could prevent the tissue changes as well as the hyperglycemia and hemoconcentration.

36. Haley, T. J., Komesu, N. and Flesher, A. M. X-Irradiation and Intestinal Ganglia (Abstract) Fed. Proc. 20: 399 (1961).

Studies were made with the Trendelenburg preparation to ascertain isolated intestinal responses to ganglionic blocking and antispasmodic drugs pre- and post-radiation. No significant differences were observed in response to hexamethonium chloride, chlorisondamine chloride, SU-1194, Pendiomide, atropine sulfate or methantheline bromide. Neither were there any alterations in amount of acetylcholine secreted by irradiated and non-irradiated intestine prior to or for three days after irradiation. It is concluded that radiation effects on intestinal tone are of central and not peripheral origin.

37. Kurstin, I. T. Effects of Ionizing Radiation on the Digestive System. (Translated by Scripta Technica, Inc.) Elsevier Publishing Co., New York (1963).

The author reviews and interprets published studies of radiation effects on the gastrointestinal system. Results of research reported in the Russian literature are covered extensively, most of these studies placing definite emphasis on the role of the nervous system in producing the various derangements studied. The important contribution of neurohumoral mechanisms regulating the activity of the digestive glands receives special emphasis.

38. Dixon, J. M. S. and Paulley, J. W.
Bacteriological and Histological Studies of the Small Intestine of Rats Treated with Mecamylamine.
Gut 4: 169-173 (1963).

The importance of motility as a factor regulating the number and distribution of bacteria throughout the gastro-intestinal tract was tested by determining the number of bacteria present in each of three segments of the small intestine of normal rats and of rats with drug-induced intestinal stasis (mecamylamine) without anatomical interference with the gut by other means. After two or three days of severely reduced peristaltic activity, the small intestine contained large numbers of E. coli throughout its length. Histological changes included increased numbers of goblet cells, shortening of villi and, in some animals, bacterial invasion of the wall of the small intestine. Return of the histological picture to normal occurred rapidly once motility was resumed.

39. Mahoney, T. D., Berlin, J. D., Pekas, J. C. and Sullivan, M. F.
The Effect of Bile on the Mucosa of the Small Intestine.
In: Gastrointestinal Radiation Injury, M. F. Sullivan, editor, Excerpta Medica Foundation, New York, pp. 42-55 (1968).

This report describes the effects of bile duct cannulation (diverting bile from the intestine) on the microscopic and ultramicroscopic (electron microscope) structure of the intestines of unirradiated and irradiated rats and swine. Bile salts have a detergent-like action. They tend to deplete the goblet cells of mucus and to reduce the thickness of the mucopolysaccharide "fuzzy coat" at the luminal borders of epithelial cells without completely stripping the cells of that characteristic covering. Bile duct cannulation and irradiation both caused an increase in thickness of the fuzzy coat although the number of goblet (mucus-secreting) cells was decreased after irradiation and increased after cannulation. Because bile salts affect intestinal motility and bacterial flora as well as mucus-secreting cells, the authors did not attempt to formulate a precise explanation of how bile and irradiation bring about the effects observed.

40. Sullivan, M. F.
Sodium, Water and B_{12} Absorption in Irradiated Rats: Influence of Bile.
In: Gastrointestinal Radiation Injury, M. F. Sullivan, editor, Excerpta Medica Foundation, N. Y. pp 216-226 (1968).

Using a specially designed perfusion apparatus, the author studied the movement of Na, H_2O and Vitamin B_{12} across the mucosa of the large and small bowel *in vivo* in normal and in x-irradiated rats (1000 R or 1500 R - ray doses). Movement of water and sodium across the mucosa is decreased to about the same extent in both directions in the irradiated rat. Absorption of vitamin B_{12} was markedly decreased. In parallel studies of the non-perfused intestine, movement of sodium from blood to lumen was increased after radiation, and the increase was greater with increasing concentrations of sodium in the lumen. Sodium from bile and other secretions would increase the sodium concentration in the lumen and also increase the transfer of sodium from blood to lumen.

41. Jackson, K. L. and Entenman, C.
The Role of Bile Secretion in the Gastrointestinal Radiation Syndrome.
Radiat. Res. 10: 67-79 (1959).

The role of bile secretion in the gastrointestinal radiation syndrome of the 1,500 R X-irradiated rat was studied. Ligation of the bile duct increased the survival time of irradiated rats and reduced the excretory loss of Na. When changes in the Na content of the gastrointestinal tract were taken into consideration, the estimated body Na loss was almost as great as the measured Na secreted in bile by irradiated rats during the same period. It is concluded that after X-irradiation of the rat with 1,500 R: (1) the loss of body Na due to net leakage of this electrolyte directly across the intestinal wall is of minor importance; (2) the major portion of the body Na loss is the result of an inadequate absorption of bile Na, which is secreted into the intestine at a normal rate; and (3) the loss of Na via the bile is an important factor in the cause of death. (Authors)

42. Hiatt, N. and Warner, N. E.
Influence of Intestinal Content on Radiation Lesions of the Small Intestine.
Proc. Soc. Exp. Med. and Biol. 124: 937-939 (1967).

The abdomens of dogs with Thiry-Vella fistulas of the jejunum (a loop of small intestine with intact blood vessels and nerves through which the intestinal content does not pass) were irradiated with 1000 and 1500 R. The post-irradiation lesions in the small intestine in continuity were typical. These included mucosal erosions with hemorrhage, reduction in the over-all thickness of the mucosa, attenuated or absent villi, an inflamed, congested lamina propria, and greater distention of mucosal glands, with stasis of mucus. The mucosal erosions, the bleeding, the flattening of the villi and the infiltration with inflammatory cells were much less conspicuous in the isolated loop. In both the fistulous and the non-fistulous small intestine, the usual post-irradiation atypias and abnormalities of intestinal epithelial cells were observed. The authors suggest that it is unlikely that mechanical factors or intestinal bacteria are involved in the differences observed, but rather, that bile or the proteolytic enzymes of the pancreas are involved.

43. Fry, R. J. M., Kisieleski, W. E., Kraft, B., Staffeldt, E. and Sullivan, M. F.
Cell Renewal in the Intestine of the Bile Duct Cannulated Rat.
In: Gastrointestinal Radiation Injury, M. F. Sullivan, editor, Excerpta Medica Foundation, N. Y. pp. 142-147 (1968).

Tritiated thymidine labeling was used to study cell renewal in the intestines of rats in which bile duct cannulations had previously been performed to divert bile from the intestine. The tritium content of duodenum and distal ileum was determined at intervals between 12 and 76 hours after injecting the label. There was no difference in the rates at which label was lost from the small intestines of cannulated and control rats. Rate of movement of labeled cells along the villi was also similar in the two groups.

44. Donati, R. M., Berman, A. R., Jervis, H. R., Stromberg, L. W. and Sprinz, H.
Absorption of Iron Following X-Irradiation of the Exteriorized Small Intestine.
Proc. Soc. Exper. Biol. Med. 130: 822-827 (1968).

The absorption of intragastrically administered radioiron was measured following exposure of the exteriorized intestinal tracts of rats to an X-ray dose of 2000 R. Each day, for five days, some rats were killed two hours after Fe administration, and total body radioiron content was measured using a small animal body counter. The gastrointestinal tract was removed, opened longitudinally and washed (physiological saline) until its radioactivity remained constant. These preparations were used in estimating iron bound to or within mucosa. Whole bowel autoradiographs were prepared using similar preparations which had first been stained in toto to demonstrate lesions and then photographed. Iron loss through the intestinal mucosa (exsorption) was estimated after intravenous administration of radioiron by total body counting of rats after their gastrointestinal tracts had been removed, washed, and returned to the carcus.

The morphologic lesion following irradiation was discontinuous. Iron absorption was increased following irradiation, apparently due to augmented absorption in areas of small intestine that did not develop morphological characteristics of severe radiation injury. Iron loss across the intestine was negligible.

45. Bond, V. P.
Effects of Radiation on Intestinal Absorption.
Amer. J. Clin. Nutr. 12: 194-204 (1963).

Effects of large radiation doses on gastrointestinal structure and function are reviewed and 51 references are cited and discussed. Sublethal doses retard gastric emptying time, affect intestinal motility and damage dividing crypt cells. Doses in the lethal range also affect motor function and crypt cells. Lesions (infection and hemorrhage) secondary to hematopoietic failure are observed during the period of granulocytopenia and thrombocytopenia. Following supra-lethal doses, mitosis of crypt cells is completely stopped and by the time death occurs (three to five days after exposure) the villi are denuded of epithelium.

Absorption of sugars, fats and electrolytes is reduced because of altered motility following lower doses, but at higher doses the reduced absorption is due to epithelial damage. The barrier function of the intestine remains relatively intact until complete denudation of villi occurs. At that time, when the animal is moribund, there may be extensive loss of fluid and electrolyte into the gut lumen.

46. Perris, A. D.
Intestinal Transport and Metabolism Following Whole Body Irradiation.
Radiat. Res. 34: 523-531 (1968).

Three days after whole body exposure to 650 R of X- or γ-radiation, the transfer of glucose, galactose and 3-O-methyl glucose across the intestine of irradiated rats was inhibited; sorbose transfer was stimulated. In contrast, previous in vitro studies of intestines of similarly irradiated rats showed that only glucose transfer was inhibited. When galactose transfer was compared (in vitro) in medium that contained glucose and medium that did not contain glucose, there was inhibition of transfer of those sugars whose transfer requires specialized active transport mechanisms. The author suggests that the radiation-induced decreases in glycolytic energy supply could account for the observed defects in transport.

47. Lengemann, F. W.
The Effect of Whole-Body X-Irradiation on the Absorption of Calcium-45 and Strontium-85 from the Intestinal Tract of the Rat.
Radiat. Res. 13: 892-897 (1960).

The author studied the effect of x-ray doses ranging from 0 R to 1000 R on the uptake of radioactive calcium and strontium by femurs of young and mature rats which received the radioisotopes (orally or intraperitoneally) eight hours after whole body irradiation. The percent of orally administered (but not intraperitoneally administered) radioisotopes of Ca and Sr found in femurs of young rats was significantly increased by x-ray doses of 200 R, although significant increases in bone uptake in mature rats was observed only after doses of 1000 R (Ca) and 400 R (Sr). The increase in absorbtion of Sr and Ca by young male rats was observed as early as two hours after irradiation and was maximal at the last time tested,

48 hours after exposure. Marked granular necrosis was observed in intestinal crypt cells of these animals two hours after exposure, but was no longer present 24 hours after exposure. Presence of food in the gut did not modify the observed effects. The author concludes that the observed radiation effect occurred at the "intestinal level".

48. Dalla Palma, L.
Intestinal Malabsorption in Patients Undergoing Abdominal Radiation Therapy.
In: Gastrointestinal Radiation Injury, M. F. Sullivan, editor, Excerpta Medica Foundation, New York, pp. 261-274 (1968).

Absorption of triolein, oleic acid, vitamin B_{12}, iron, D-xylose and glucose was measured before, during and following completion of a course of radiation therapy to the abdomen in a group of women afflicted with cancer of the genital organs. The radiation was from a ^{60}Co source, delivered in daily treatments of 150-200 R until a total dose of 4000-5000 R was reached (five weeks). Some patients developed gastrointestinal symptoms. It was found that malabsorption of fats, sugars, iron and vitamin B_{12} frequently developed during the course of therapy although it tended to level off in severity or even improve during the later part of the course. Incidence and severity of malabsorption were not clearly correlated with radiation dose, but a well functioning intestine was found more likely to be damaged by radiation than was an impaired intestine.

49. Duncan, W. and Leonard, J. C.
The Malabsorption Syndrome Following Radiotherapy.
Quart. J. Med., New Series 34: 319-327 (1965).

Six patients are described who have developed a malabsorption syndrome after radiotherapy for malignant disease in the abdomen. Diarrhoea, wasting, intestinal obstruction, steatorrhoea, and megaloblastic anaemia were the main clinical features; one patient had subacute combined degeneration of the spinal cord.

There is experimental support for the contention that radiation damage to the small bowel may occasionally cause a malabsorption syndrome. The pathological changes include widespread ulceration of the small intestine, with

diffuse inflammatory change, endarteritis, fibrosis, and the development of strictures. The ileum is especially likely to be damaged by high-dose pelvic irradiation. Two of our patients had strictures, and the remainder probably had diffuse inflammatory and fibrotic changes in the ileum. (Authors)

50. Trier, J. A., Browning, T. H. and Foroozan, P. The Effects of X-Ray Therapy on the Morphology of the Mucosa of the Human Small Intestine. In: Gastrointestinal Radiation Injury, M. F. Sullivan, editor, Excerpta Medica Foundation, N. Y. pp. 57-71 (1968).

Serial changes in histology and function of the irradiated intestine were studied by obtaining a total of 112 peroral biopsies from 9 patients receiving 1000 kV X-ray therapy to the abdomen. Doses ranged from 2000-3000 R for five or six days a week. Tissue sections were examined by conventional and electronmicroscopy. The doses used caused a decrease in mitotic activity and megalocytosis of epithelial cells, a decrease in absorptive surface of the bowel, infiltration of the lamina propria with inflammatory cells and the formation of a few small crypt abcesses. At the time that the histological changes were most pronounced, the absorption of xylose and glucose through the irradiated segments was decreased. Histological and physiological lesions healed rapidly and completely following cessation of therapy. Unirradiated segments of bowel were not affected.

51. Lushbaugh, C. C., Sutton, J. and Richmond, C. R. The Question of Electrolyte Loss in the Intestinal Death Syndrome of Radiation Damage. Radiat. Res. 13: 814-824 (1960).

Sodium and potassium balance was studied in rats receiving 700, 1000, 2000, 2100, 5000, or 8000 R of X-rays as a single dose delivered to the entire body. All rats that received 2000 R or more died between 80 and 90 hours after exposure from the acute intestinal radiation syndrome. Radioactive Na and K and whole-body radioactivity counting were used in the electrolyte balance studies.

Conservation of total body Na and K during fasting was not altered by X-ray doses as great as 8000 R, and "no evidence was found to support the conjecture that an

increased sodium loss from the whole body either is caused directly by radiation or plays a primary role in the "intestinal death syndrome" of radiation damage. Loss of electrolyte-containing fluids into the intestinal tract in this syndrome appears from this study to be a terminal phenomenon secondary to denudation of the intestinal mucosa with which it coincides."

52. Valeriote, F. A. and Baker, D. G.
The Combined Effects of Thermal Trauma and X-irradiation on Early Mortality.
Radiat. Res. 22: 693-702 (1964).

Male albino rats originally of Wistar strain, were exposed to whole body X-irradiation at doses of 550 to 750 R and/or to thermal trauma over 16% of body surface for 1 or 1.5 min., producing second- to third-degree burns. Those animals that died between 0 and 8 days after treatment, with continual weight loss, were classified as "gastrointestinal-like" deaths. Those that died between 8 and 20 days after treatment or gained weight at any time before death were classified as "bone marrow" type deaths. Results show that "the administration of a sublethal thermal trauma...caused a significant decrease in survival in rats exposed to X-ray doses between 550 and 750 R. The increase in mortality in the case of the combined injuries was confined to the time period characteristic of injury to the gastrointestinal tract - that is, to 3 to 8 days after X-irradiation." To test the hypothesis that the synergistic effect of thermal trauma on x-irradiation is due to a bacteremia, two groups of rats were given 5 mg of Aureomycin per day for 7 days following treatment. One of these groups had received 700 R of radiation, and the other had received 700 R plus a 1-minute burn. The antibiotic therapy produced no change in mortality. Water consumption and urine volume were recorded daily for the first 8 days after injury; both decreased after X-irradiation, then approached normal again by days 6 to 7. Addition of thermal trauma did not alter this effect significantly. Since other workers using different strains of rats have reported polydipsia and polyuria as effects of X-irradiation, it is suggested that these effects are strain-dependent. Thermal trauma without irradiation produced polydipsia and polyuria.

53. Carroll, H. W. and Kimeldorf, D. J.
Protection Through Parabiosis against the Lethal Effects of Exposure to Large Doses of X-Rays.
Science 156: 954-955 (1967).

Parabiotic rat pairs with a skin-vascular anastomosis were used to test whether shielding of one member of the pair would protect the irradiated partner against exposure to very large doses of X-rays (1200 to 2400 roentgens). Except with the lowest dose, all unshielded, irradiated pairs or single irradiated animals died before 5 days had elapsed. In contrast, irradiated rats that had a shielded parabiont partner survived the 5-day period and many survived beyond 30 days. This is interpreted as protection against the acute intestinal death that normally occurs in the dose range investigated. The authors speculate that the supportive action of the shielded parabiont on the irradiated partner is probably through maintenance of fluid and electrolyte balance during the critical period, and possibly through prevention of disseminated infection. They also suggest that the high 30-day survival rate may reflect the role of the shielded partner as a source of hematopoietic stem cells, providing "hematopoietic support".

54. Walburg, H. E. Jr., Mynatt, Edna I. and Robia, D. M.
The Effect of Strain and Diet on the Thirty-Day Mortality of X-Irradiated Germfree Mice.
Radiat. Res. 27: 616-629 (1966).

This report describes differences in the $LD_{50/30}$ of X-irradiated germ-free and conventional mice of different strains and an increase in the $LD_{50/30}$ of germ-free mice receiving a liquid diet supplement instead of water.

Strain differences in radiosensitivity were observed (and have been observed by others). The variation in $LD_{50/30}$ among germ-free mice of various strains was only half that observed among the same strain of conventional mice, indicating that micro-flora play a role in determination of strain radiosensitivity. Genetic background is also important. Although survival time of irradiated germ-free mice was always somewhat longer than similarly irradiated controls of the same strain, among the germ-free strains studied, one had a mean survival time 3-6 days shorter than that of the other strains. The liquid supplement increased the "radioresistance" of

germ-free mice (raised the $LD_{50/30}$, lengthened survival time, decreased slope of mortality curve). The supplement did not alter radioresistance of conventional mice; however, the authors feel this can be explained by the presence of bacteria in the feces of the mice, a ready source of dietary nutrients for coprophagic animals.

55. Fulton, M.
Imbalance of the Normal Microbial Flora. Microbial Interactions in Gastroenteritis.
Amer. J. Digest. Dis. 10: 870-872 (1965).

The author deplores the extreme paucity of information concerning the interrelationships of normal flora and the pathogenic organisms in health and in gastroenteritis. The alterations that may occur in normal flora where the gut is invaded by pathogenic bacteria is usually ignored and accepted as coincidental in the etiology and development of acute gastroenteritis due to organisms such as Salmonella and Shigella. Usual plating methods used in identifying fecal flora are not quantitative and do not indicate "whether the pathogen represents an added element or whether it has replaced part of the normal flora." He cites several studies of epidemics of severe diarrhea to illustrate this point.

Use of broad spectrum antibiotics has provided inadvertent experimental evidence that suppression of normal flora provides an opportunity for pathogenic activity by other microorganisms. Experimental studies now confirm some of these observations, e.g. if mice are treated with streptomycin, Salmonella infection occurs because of virtual elimination of anaerobic gram-negative bacilli of the Bacteroides group. He sums up current ignorance of bowel ecology thus: "There is increasing demand for more extensive data on the microbial flora of the intestinal tract in health and disease. Here the microbiologist faces large technical and interdisciplinary problems. Most of the kinds of bacteria inhabiting the intestine have received only sporadic attention in diagnostic bacteriology. The virus population of the intestine is also poorly characterized. The physiology and growth characteristics of the intestinal microflora are so varied that few bacteriologists are skilled in the isolation and identification of more than one group."

56. Savage, D. C., Dubos, R. and Schaedler, R. W.
The Gastrointestinal Epithelium and its Autochthonous Flora.
J. Exper. Med. 127: 67-76 (1968).

Various strains of bacteria of the normal flora become established in the different areas of the gut of mice according to a definite time sequence. These bacteria which escape detection when conventional techniques are applied in sampling are intimately associated with the wall of the gut; they have evolved with their mouse host and constitute its autochthonous flora. The flora differs qualitatively from one mouse colony to another. The various species of autochthonous bacteria are highly selective with respect to their anatomical location. Autochthonous lactobacilli, for example, are numerous on the squamous epithelium of the stomach. (The existence of squamous epithelium in certain portions of the stomach of a wide variety of mammals is, in itself, a surprising observation.) Strictly anaerobic bacteroids and fusiform bacilli are the characteristic autochthonous flora of the large intestine. They can be cultured from tissue homogenates made after the surface has been washed repeatedly.

"For a full understanding of the ecology of the normal microflora, it is necessary to think of body surfaces as distinct microenvironments in which virtually pure cultures of a few species of microorganisms interact with their host and the adjacent microbial populations."

57. Schaedler, R. W., Dubos, R. and Costello, R.
The Development of the Bacterial Flora in the Gastrointestinal Tract of Mice.
J. Exper. Med. 122: 59-66 (1966).

The author describes media, equipment and techniques developed to facilitate quantitative enumeration of various aerobic and anaerobic bacterial species present in the stomach and small and large intestines of NCS Swiss mice maintained under special conditions in their laboratory. The same strain maintained under standard conditions plus a few other strains were also studied during the six-year investigation. The evolution of the gastrointestinal flora was studied by analyzing the flora in homogenates of various parts of the gastrointestinal tract at daily intervals from the time of birth to time of weaning.

The fetus was found to be essentially free of organisms at birth, but very shortly thereafter lactobacilli and anaerobic streptococci became established and persisted in large numbers in the stomach and small intestine as well as in the colon. Anaerobic bacilli of the bacteriodes group became established only in the 16th day. Other bacterial species also became established and the changes in relative numbers of the various organisms are documented.

58. Dubos, R. J. and Schaedler, R. W.
The Effect of the Intestinal Flora on the Growth Rate of Mice and on Their Susceptibility to Experimental Infections.
J. Exper. Med. 111: 407-417 (1960).

A colony of albino mice (NCS) derived from Swiss albino mice was developed starting with offspring, delivered by sterile Caesarian section, nursed by a colony of another strain known to be free of both PPLO organisms and the virus of enzootic bronchiectosis. These mice were maintained free of intestinal and ectoparasites and have been kept in a "protected" environment that prevents contact with outside sources of infection. The characteristic intestinal flora of the mice differs qualitatively from that of the parent colony, lacking in particular the Gram-negative lactose fermenters (E. coli) that are always found in mice of the parent colony. The NCS mice grew more rapidly than ordinary mice on complete diets and continued to gain weight slowly even on deficient diets that caused ordinary mice to lose weight. They were more susceptible than ordinary mice to certain bacterial infections (K. pneumoniae and S. aureus), but much more resistant to the lethal effect of large doses of endotoxin, although endotoxin in very small doses increased their susceptibility to staphylococcal infection. Contamination of NCS mice with E. coli from the ordinary colony caused them to acquire the characteristics of the ordinary mice.

59. VanWoert, M. H.
Proteus Mirabilis Enterocolitis Following Abdominal Irradiation.
Amer. J. Digest. Dis. 12: 737-741 (1967).

Proteus bacteria are frequently present as saprophytes in the normal intestinal tract and almost never cause symptoms in the adult unless the bacterial flora has been altered by broad-spectrum antibiotics. In the case described in this report, irradiation of the intestine appeared to have unleashed the otherwise controlled growth of the organism. The patient was a 52 year old woman who received a four-week course of radiation therapy (^{60}Co γ-rays; total skin dose 2420 R) to the lower abdomen following surgery for removal of ovarian cystadenoma. She developed nausea after 2 1/2 weeks of therapy; vomiting and diarrhea one week later. Symptoms increased in severity and were associated with large amounts of flatus, colicky pain, severe dehydration requiring intravenous administration of fluids at home, and weight loss. There was marked gaseous distension of large and small bowel. Proteus mirabilis was the predominating organism in several stool cultures. The organism was sensitive to nalidixic acid *in vitro* and therapy with that agent for ten days controlled the infection. Return of usual intestinal flora paralleled the clinical improvement.

60. Fritz, T., Brennan, P. C., Giolitto, J. A. and Flynn, R. J.
Interrelationships Between X-Irradiation and the Intestinal Flora of Mice.
In: *Acute Gastrointestinal Radiation Injury*, M. F. Sullivan, editor, Excerpta Medica Foundation, N. Y. pp. 279-290 (1968).

The geometric mean count of bacteria in various sections of small bowel varies as a function of distance from the pylcris. The slopes of the increase were measured for various types of bacteria in a pathogen-free strain of mice. The experimental variables studied were whole body exposure to 900 R of X-rays, exposure to 500, 600 or 700 R of X-rays plus intragastric inoculation with *Citrobacter freundii*, and inoculation with *C. freundii* only. In every instance, mice in the groups irradiated and infected died earlier and in greater numbers than those irradiated but not infected. Some changes could be demonstrated in flora of mice infected with *C. freundii*, but they were

not sufficient to explain the results of the survival experiment. The non-pathogenic C. freundii clearly exerted a "deciding influence on radiation toxicity."

61. Furth, F. W., Coulter, M. P. and Howland, J. W.
Bacteriologic Studies of the X-Radiated Dog.
Amer. J. Pathol. 28: 171-183 (1952).

Twenty-four adult dogs received 450 R of total body x-radiation. Of these dogs, 12 received aureomycin at the rate of 100 mg. per kg. per 24 hours, for 28 days following radiation. Twelve animals exposed simultaneously served as controls. Bacteriologic studies of blood necropsy material, and feces of radiated and normal dogs were made.

The incidence of positive blood cultures post-radiation was greater in the control group than in the treated group.

The fecal coliform bacteria, staphylococci, and streptococci increased to a greater extent post-radiation in the treated than in the control group.

Aureomycin resistant organisms were obtained from necropsy cultures from the treated dogs. The bacteria isolated from the control dogs were sensitive to aureomycin. The sensitivity to aureomycin of the fecal coliform bacteria and streptococci decreased post-radiation in the treated dogs. Bacterial strains resistant to high concentrations of aureomycin developed. (Authors)

62. Altmeier, W. A.
Bodily Response to Infectious Agents.
J. Amer. Med. Assoc. 202: 1085-1092 (1967).

This discussion reviews briefly and clearly the great variety of ways in which septicemia may disrupt body functions and cause death. The author cites several types of data to illustrate how important it is for the physician to understand the broader implications of severe infection and to be well educated with respect to proper use of antibiotics, including the hazards associated with abuse of antibiotic therapy.

63. Stoner, R. D., Hess, M. W. and Bond, V. P. Radiation and Infection, An Annotated Bibliography Prepared for Commission on Radiation and Infection, Armed Forces Epidemiological Board, Department of Defense, Office of the Surgeon General, Department of the Army, Washington, D. C. (1965).

A total of 819 abstracts and cross references of the world's published literature concerning effects of ionizing radiation on infection and immune mechanisms is presented.

64. Balish, E.
pp. 14-17 in ORAU-101. Medical Division Report, Oak Ridge Associated Universities, Inc., Tenn. (1967).

Patients receiving radiation therapy over the entire body were the subject of this study. A dose of 100 R of γ-radiation was sufficient to alter the fecal, gastric and nasal microflora and the pH of gastric secretions within one to twelve days after exposure.

65. Rosenberg, J. C. and Rush, B. F.
Lethal Endotoxin Shock. Oxygen Deficit, Lactic Acid Levels and Other Metabolic Changes.
JAMA 196:767-769 (1966).

A number of physiological and biochemical parameters were measured serially in anesthetized dogs before and after intravenous injection of a lethal dose of E. coli endotoxin (4 mg/kg). Mean survival time of the 10 dogs was 352 ± 141 minutes. All dogs developed oxygen deficit, the linear increase in deficit corresponding to: the fall in blood pressure, mixed venous oxygen saturation and progressive deterioration of the clinical condition. Endotoxin shock differed from hemorrhagic shock with respect to the correlation between oxygen deficit and lactic acid and lactate values, the excess lactic acid and lactate levels being relatively modest in endotoxin shock. The absence of excessive elevation of arterial lactic acid concentration suggests that endotoxin has toxic effect on cellular metabolism, inhibiting anaerobic glycolysis and depriving the cell of energy.

66. Lillehei, R. C., Dietzman, R. H., Movsas, S. and Bloch, J. H.
Treatment of Septic Shock.
Modern Treatment 4: 321-346 (1967).

Endotoxins are lipopolysaccharides, present in the walls of all gram-negative bacteria, which exert a variety of effects, determined in part by dosage, once they are released into the circulation. Results observed following injection of endotoxin include release of histamine, serotonin, epinephrine and norepinephrine; the peripheral stores of catecholamines are depleted; vascular sensitivity is profoundly affected, resulting ultimately in vasodilation, pooling of blood and shock. The tissues affected are those with vasculature innervated by sympathetic fibers (alpha receptors) and sensitive to sympathomimetic agents. Neurotoxic effects are also observed and are an early sign of impending shock.

In the last decade, gram-negative bacterial infections have become the principal cause of death from septicemia. The authors stress the importance of antibiotic resistance of increasing numbers of gram-negative organisms and indicate that the increasing prevalence of this characteristic is due in large part to promiscuous use of antibiotics.

The clinical and laboratory findings in endotoxin shock are described and compared with those in shock of other etiology. Treatment is discussed, including measures necessary to support respiration and circulation, with emphasis on the use of corticosteroids and intravenously administered fluids. Serial measures of central venous pressure, blood pressure and urine output are very helpful as guides to fluid requirement. Digitalis is administered if cardiac failure occurs; potassium supplements for hypokalemia. Identifying the source of infection promptly (culturing all available sources) and vigorous, appropriate antibiotic therapy are essential.

The authors have used phenoxybenzamine (a potent alpha adrenergic blocking agent) with remarkable success in the treatment of endotoxin shock in dogs, but this agent is available for investigational use only. Drugs that are sympathomimetic in action only intensify the visceral ischemia. Choice of antibiotics is also discussed. The importance of preventing shock is emphasized

including the possibility of inducing tolerance to endotoxin in those patients having a high risk of suffering shock, "such as the military, surgical patients, and patients who are 'coronary prone'."

67. Melnick, I. and Litvak, A.
Gram-Negative Bacteremia: An Evaluation of Fifty-Nine Cases During 1963.
J. of Urology 96: 257-262 (1966).

The authors reviewed fifty-nine cases of gram-negative bacteremia (in adults) in which positive blood cultures were obtained. These cases were all studied in the Philadelphia General Hospital during 1963. Mortality rate was 67% for the 36 male patients; 39% for 23 female patients (who represented a younger group, many of them on the obstetrical and gynecological services). Data are analyzed with respect to portal of entry of bacteria, underlying disease, organism cultured from blood and relationship of organism to mortality and shock. Shock and oliguria were found in this study as in others to be ominous signs in gram-negative bacteremia. Mortality rate was 70% if hypotension occurred; 47% if it did not. Therapy consists of appropriate, vigorous antibiotic therapy plus intravenous fluid and other supportive therapy as necessary. With respect to the treatment of shock, vasopressor agents alone gave lowest survival rates; vasopressor agents plus corticoids, the highest. Suggestions are made for a therapeutic regimen that may possibly prove more effective than that previously employed.

68. Vick, J. A., DeGraaf, R. and Berdjis, C. C.
Interaction of Ionizing Radiation and E. coli Endotoxin. I. Effect of Radiation on Endotoxin Shock.
Mil. Med. 133: 387-90 (1968).

Both irradiation and endotoxin have effects on the blood and hematopoietic system, endotoxin acting by way of an intermediate reaction with a heat-labile serum factor. Possible interaction of radiation and endotoxin was studied in an experiment utilizing dogs. The experimental groups studied were as follows:

No. dogs	Radiation dose	Endotoxin administered
6	1000 R	-----
12	1000 R	1.0 mg/kg 30 min. after exposure
14	1000 R	1.0 mg/kg 2 hrs. after exposure
6	---	1.0 mg kg endotoxin

Survival data showed that irradiation 30 minutes or two hours before endotoxin injection prolonged the survival time and modified (suppressed) the blood pressure changes in endotoxin-treated animals.

69. Zweifach, B. W. and Thomas, L.
The Relation Between the Vascular Manifestations of Shock Produced by Endotoxin, Trauma and Hemorrhage.
I. Certain Similarities Between the Reactions in Normal and Endotoxin-Tolerant Rats.
II. The Possible Role of the Reticulo-Endothelial System in Resistance to Each Type of Shock.
J. Exper. Med. 106: 385-414 (1957).

Derangement of peripheral circulation resulting in irreversible failure of circulatory homeostasis is the final stage before death in hemorrhagic shock. Similarities between vascular reactions in hemorrhagic or traumatic (conventional) shock and those produced by lethal doses of endotoxin (from E. coli) are presented in this report. In all three types of shock there is profound inhibition of arteriolar and pre-capillary reactivity to topical epinephrine following an initial stage of hyperreactivity; small veins fail to relax completely after constrictor doses of epinephrine and terminal vessels develop an unusual sensitivity to fluctuation in temperature of fluid irrigating the tissue. The fundamental similarity of the reactions is shown by:

1. The nearly identical alterations in microcirculation (especially response to epinephrine) culminating in profound hyporeactivity.

2. Animals rendered tolerant to endotoxins also show increased resistance to hemorrhagic and traumatic shock. (The reverse is not always observed, however.)

3. Small doses of endotoxin are sufficient to convert non-lethal hemorrhagic shock into "irreversible", fatal shock.

Measures that induce "blockade" of the reticuloendothelial system (RES) are shown to exacerbate the vascular effects of bacterial endotoxin and to counteract the cross-tolerance induced by endotoxins against lethal effects of hemorrhage or drum trauma. Vascular reactions characteristic of irreversible hemorrhagic shock can be simulated by a combination of pre-treatments with particulate material and infusion of small doses of endotoxin. Repeated injections of particulates (colloids) increased the phagocytic activity of the RES and enhanced tolerance of shock. Although carbon clearance was enhanced in rats with induced tolerance to endotoxins, it was not enhanced in rats made resistant to trauma. The authors suggest that the RES is of central importance in all three types of shock but that its participation is not necessarily linked to its phagocytic activity.

70. Lillehei, R. C., Longerbeam, J. K. and Bloch, J. H.
Physiology and Therapy of Bacteremic Shock.
Experimental and Clinical Observations.
Am. J. Cardiol. 12: 599-613 (1963).

The authors have studied the physiology of endotoxin shock in dogs extensively and this report is a comprehensive summary of their findings. The increased resistance of the perfused intestine in endotoxin shock is even greater than that observed in hemorrhagic shock, even when postcaval shunt has been established to bypass the liver. The impressive therapeutic success achieved with Dibenzyline (0.5-1 mg/Kg) (plus fluid replacement) is described.

71. Barksdale, W. L. and Ghoda, A.
Agglutinating Antibodies in Serum and Feces.
J. Immunology 66: 395-401 (1951).

Sonne dysentery and a case of Flexner dysentery in which there was no bleeding into the bowel were studied with respect to the production of serum and fecal antibodies (coproantibodies).

The experimental results demonstrate that the fecal and serum antibodies are qualitatively different as well as

being different with respect to the time at which they first appear; fecal antibodies appearing early, and serum antibodies later. Fecal extracts from Sonne dysentery contained antibodies (agglutinins) against both I and II phase antigens, whereas serum contained only antibodies against sonnei I antigen. The authors also observed complete absence of sonnei phase II agglutinins in serum from other patients with Sonne dysentery.

In Flexner dysentery, fecal extracts consistently agglutinated phase B antigen in higher dilutions than the phase A antigen; the reverse was true for serum antibody.

72. Visek, W. J. and Dang, H. C.
Protection Against Lethal Doses of Gamma Irradiation with Urease Immunity.
A Research Report from Cornell Agricultural Experiment Station, New York State College of Agriculture, Ithaca, N. Y. April 1966.

Mice were made immune to urease by active immunization with the crystalline enzyme or passive immunization with rabbit anti-urease serum (0.4 ml 10 minutes before exposure to radiation or 0.3 ml three times a week for two weeks, the last injection 6 days before irradiation). After exposure to 800 R of ^{60}Co γ-radiation, 72.8% of the immunized animals survived, in contrast to 21% of the non-immunized control mice. The $LD_{50/30}$ was raised from 600 R to 860 R by the immunization. Protective effects were compared with those of S, beta-aminoethylisothiouronium Br • HBr and β-mercaptoethylamine HCl which also inhibit urease. It is suggested that ammonia is an important toxin in irradiation death.

73. Visek, W. J. and Dang, H. C.
Urease Immunity in Irradiation Injury with Consideration of Growth and Liver Insufficiency.
In: Gastrointestinal Radiation Injury, M. F. Sullivan, editor, Excerpta Medica Foundation, N. Y. pp. 292-300 (1968).

Treatment of mice with rabbit antiurease serum prior to exposure to 800 R (LD_{90}) gave an average increase in survival over control animals of 50% and raised the $LD_{50/30}$ from 600 R to 800 R. The authors discuss the rationale for this approach to protection against radiation injury, pointing out that ammonia has well-known cytotoxic

effects. Feeding urea to mice results in histological changes in the wall and mucosa of the intestine. This may be prevented by feeding 100 ppm of chlortetracycline with the urea. The antibiotic inhibits growth of bacteria that produce urease which then acts on urea to yield ammonia. As little as 20 ppm of ammonia in inspired air will alter respiratory epithelium sufficiently to produce a definite increase in the incidence of pulmonary viral infections. Liver disease, renal disease and acute radiation injury are all associated with aberration of cell proliferation. In the first two of these, high blood ammonia concentrations are also found; there is virtually no information about this variable in severe acute radiation injury.

On this basis, the authors considered that in the presence of increased blood urea nitrogen levels after heavy irradiation + accumulation of fluids and increased bacterial growth in the intestine, conditions were right for increased ammonia production.

74. Hampton, J. C., and Rosario, B.
Distribution of Exogenous Peroxidase in Irradiated Mouse Intestine.
Radiat. Res. 34: 209-27 (1968).

Within 10 minutes after intravenous injection, horseradish peroxidase was found in the lamina propria and in the intestinal epithelium, both in intercellular spaces and within the cytoplasm of epithelial cells. Examination of intestines of mice subjected to 3 krads of x radiation and sacrificed at 24-hour intervals up to four days revealed that most intact capillaries remained patent and were permeable to peroxidase. It was not possible to characterize damage to endothelial cells on a morphological basis alone, but definite changes in permeability to peroxidase were demonstrated. Neither capillary nor epithelial basement membranes seemed to constitute a significant barrier to the extra-vascular diffusion of peroxidase, but at the time of villus denudation, on day four, epithelial basement membranes were disrupted in the denuded areas. Diffuse staining of epithelial cell cytoplasm by peroxidase reaction product and less accumulation of it in intercellular spaces within the epithelium was observed on days three and four postirradiation. Neither evidence of leakage through, nor secretion by, epithelial cells of

peroxidase into the gut lumen nor localization within lacteals was detected. Some of the enzyme probably was secreted or diffused into the lumen before denudation occurred but escaped detection by being washed away by the tissue fixative. (Author)

75. Morgenstern, L. and Hiatt, N.
Injurious Effect of Pancreatic Secretions on Postradiation Enteropathy.
Gastroenterology 53: 923-929 (1967).

The authors studied gastrointestinal injury in dogs following exposure of the abdomen to an X-ray dose of 1500 R. Four experimental groups were prepared (surgically) so that the small intestine of each group was in contact with different digestive secretions as follows:

1. A segment of small intestine from pyloris to entry of Roux-en-Y loup was in contact with pancreatic secretion and its intrinsic secretions.

2. Small intestine between Roux-en-Y loop to ileocecal valve was in contact with pancreatic juice, bile and intrinsic secretions.

3. Small intestine in dog with Roux-en-Y cholecystojejunostomy was in contact with bile and intrinsic secretions.

4. Small intestine in contact only with its intrinsic secretions (Thiry-Vella fistula).

Clinically, all four groups of animals reacted as did unoperated dogs receiving the same radiation dose to the abdomen. At autopsy, however, there were striking differences in the small intestines in the various groups. Groups 1 and 2 (above) showed the same severe damage as did the unoperated dogs. In groups 3 and 4 the damage was much less, consisting largely of changes secondary to inhibition of mitosis and aberrant mitosis. The authors conclude that pancreatic secretions are the major cause of the total devastation seen in the small intestine in the radiation-induced gastrointestinal syndrome. They suggest, "If methods were developed

either to divert or to neutralize the injurious element in pancreatic secretion, the lethality of large doses of radiation----should be considerably diminished."

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Proc. Soc. Expr. Biol. Med. 77: 715-718 (1951).

No change in absorption of radioactively labeled protein occurred in mice exposed to 600 R of X-rays, although a change in tonus and motility of the gastrointestinal tract was observed.

77. Symposium on Comparitive and Interactive Effects of Radiation and Drugs, held May 23, 1965.
Radiat. Res. 30: 329-443 (1967).

This is a set of nine papers presented at a symposium held during the 13th annual meeting of the Radiation Research Society in Philadelphia. References 78 and 82 are abstracted separately. Other papers are concerned with the general problem of modification of pharmacological activity following irradiation, radiation effects on electro-convulsive thresholds and on olfactory cortex, humoral factors in radiation-induced motivation, and other subjects.

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Central Nervous System Drugs and X-Irradiation: Their Interactive Effects.
Radiat. Res. 30: 351-358 (1967).

The toxicity of a range of doses of racemic amphetamine sulfate, chloralose, pentylenetetrazol, sodium pentobarbital and strychnine sulfate was studied in normal 20 gram female Swiss Albino mice that received a X-ray dose of 120 R over a period of one hour prior to the injection of the drug. Non-irradiated mice served as controls. Irradiation increased the lethal effect of amphetamine and pentylenetetrazol, decreased the lethal effect of chloralose and pentobarbital and had no effect on the lethality of strychnine.

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Radiat. Res. 29: 121-130 (1966).

Oxidative phosphorylation in mitochondria isolated from livers of mature rats was measured three to four hours after whole body irradiation with 1000 R of X-rays. The authors found no impairment of oxidative phosphorylation in male or female rats in any of the ages or strains studied. These results agreed with their earlier studies and with those of most, but not of all, other investigators. They suggest that the discrepancies may reflect differences in extramitochondrial cellular activities in the various experiments.

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Oxidation by liver preparations from rabbits was not significantly altered by whole body exposure of the animals to 500 rads of X-ray, although the rate of oxidation by thymus preparations from irradiated rabbits was less than 1/3 of that found in thymus preparations from unirradiated controls.

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In this extension of previous studies, structural integrity of the cytoplasmic membranes (including mitochondrial membranes) of tumor cells was markedly altered by X-ray doses of 3000 R localized to the tumor area, although doses as large as 10,000 R failed to affect the mitochondrial oxidative metabolism. Electron microscopic changes observed were largely mitochondrial. The authors conclude, "Radiation injury induced in the membrane system may cause acute cell death. Conversely, mitochondrial oxidative metabolism does not seem to play a significant role in primary radiation damage, at least where the experimental material herein reported is concerned."

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Effects of X-Irradiation on the Hexobarbital-metabolizing Enzyme System of Rat Liver.
Radiat. Res. 31: 315-326 (1967).

Normal weaning 23-day old male rats show rapid increases in the activity of the hepatic microsomal enzyme that catalyzes the oxidative metabolism of hexobarbital. Development of this enzyme, which normally occurs from 21 to approximately 45 days after birth is inhibited if the 23 day old animals receive whole-body exposure to 400 R of X-rays or if they are irradiated over the head only. Hypophysectomy also inhibits development of the enzyme system. The authors have previously obtained similar results in studies of other microsomal enzymes, suggesting an indirect effect of radiation on some process involved in enzyme synthesis.

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Effect of X-Rays on Glucuronide Synthesis by Gastric Mucous Membrane.
Acta physiol. scand. 43: 77-81 (1958).

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13. ABSTRACT This technical report is the third in a series of three reviews of promising research opportunities to improve the treatment of ionizing radiation injury in the soldier. It complements the first report on A Study of the Immunologic Aspects of Therapy of Radiation Injury in the Soldier, AD 674262, and A Study of Early Radiation-Induced Biological Changes as Indicators of Radiation Injury, AD 685840.

Early symptoms produced by radiation exposure are related to the abnormal physiology and cellular lesions of the gastrointestinal tract. These symptoms have diagnostic value but the pathologic changes are not readily amenable to medical treatment. This report reviews recent research on the effects of radiation on the gastrointestinal tract of man and experimental animals including: gastrointestinal symptomatology; immediate post-irradiation cellular events; morphologic responses; gastrointestinal and hematopoietic correlations; intestinal motility and malabsorption; intestinal flora changes; antibiotics in radiation therapy; radiation-induced vomiting; transport of fluid, electrolytes, nutrients, and other essential elements; and alterations in drug metabolism. In reviewing these aspects of the radiation-induced "gastrointestinal syndrome" therapeutic opportunities are identified. Suggested areas for future research emphasis are summarized.

A critical literature review entitled The Gastrointestinal Syndrome in Acute Radiation Injury and an annotated evaluative bibliography constitute Part II of the report.

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Gastrointestinal and Hematopoietic Correlations						
Gastrointestinal Symptomatology						
Immediate Post-Irradiation Cellular Events						
Induced Vomiting						
Intestinal Flora Changes						
Intestinal Motility and Malabsorption						
Morphologic Responses						
Treatment of Radiation Injury						